

CLINICAL PRACTICE GUIDELINE

The 2024 revised clinical guidelines on the management of thyroid tumors by the Japan Association of Endocrine Surgery

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Abstract. The Japan Association of Endocrine Surgery published the first edition of the “Clinical guidelines on the management of thyroid tumors” in 2010 and the revised edition in 2018. The guideline presented herein is the English translation of the revised third edition, issued in 2024. The aim is to enhance health outcomes for patients suffering from thyroid tumors by facilitating evidence-based shared decision-making between healthcare providers and patients, as well as standardizing the management of thyroid tumors. The focus is on adult patients with thyroid tumors, addressing clinically significant issues categorized into areas such as an overview of the diagnosis and treatment of thyroid nodules, treatment strategies by histological type, radioactive iodine therapy, treatment of advanced differentiated carcinoma, pharmacotherapy, and complications and safety management associated with thyroid surgery. Thirty-two clinical questions were established in these areas. Following a comprehensive search of the literature and systematic review to evaluate the overall evidence, we aimed to present optimal recommendations by considering the balance of benefits and harms from the patient's perspective. We integrated evidence and clinical experience to determine the “Certainty of evidence” and “Strength of recommendations”. Based on these, we illustrated overall flows of care as “Clinical algorithms”. Necessary background knowledge of diseases and established clinical procedures for understanding the recommendations are presented in “Notes”, while information that may be clinically useful but for which evidence remains insufficient is included in “Columns”, based on the current state of evidence. Finally, future challenges for the next revision are presented as “Future research questions”.

Key words: Guideline, Thyroid tumor, Thyroid cancer, Japan Association of Endocrine Surgery, Evidence-based medicine

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Introduction

This guideline is the third revised edition of the “Thyroid Tumor Management Guidelines” published in 2010 by the Japan Association of Endocrine Surgery (JAES) and the Japanese Society of Thyroid Surgery, and the “Thyroid Tumor Management Guidelines 2018” published in 2018. These guidelines are primarily aimed at adult patients. The evidence-based medicine (EBM) and standardization of treatment that the first edition aimed for have become increasingly important in clinical

practice. In addition, significant amounts of new evidence have been accumulated, particularly in the form of notable advances in pharmacotherapies. To fulfill the objectives of the guideline, this revised edition has been published to incorporate these evolutions.

Objective

The objective of this guideline remains unchanged since the initial edition in 2010: to improve health outcomes for patients suffering from thyroid tumors. This revised edition also aims to facilitate evidence-based shared decision-making between healthcare users and providers and to standardize the management of thyroid tumors. To achieve this, the guideline incorporates a systematic review to evaluate the overall body of evidence and provide recommendations that balance intended benefits and potential harms from the perspective of patient health. However, in this field, various areas remain in which high-quality evidence is lacking, despite their clinical significance. The goal is to provide a practical guideline based on the current consensus.

Applicability of the guideline

This guideline is expected to be utilized in medical scenarios involving the initial evaluation, diagnosis, treatment, and follow-up of thyroid tumors. Specifically, the guideline focuses on thyroid tumors and does not address non-tumorous nodules (such as Hashimoto's disease or inflammatory conditions) or lymphomas. The guideline is intended for adult patients and generally excludes pediatric cases. The primary users of this guideline intended to be clinicians and healthcare staff dealing with thyroid disorders.

Guideline development group

The guideline was developed under the supervision of the JAES. The guideline development committee consisted of one chairperson, two vice-chairpersons, and seven members. The specialty of the members included six surgeons, two radiologists/nuclear medicine specialists, one medical oncologist, and one pathologist. Additionally, there was one observer. A systematic review team of 49 members also participated in the development process.

Regarding conflicts of interest, members of the guideline development group and external review committee reported their financial disclosures in accordance with the conflict-of-interest guidelines of the JAES for the past three years.

Development methodology

The revision work for the guideline commenced in October 2021. This process involved dividing clinically significant issues into categories: an overview of the diagnosis and treatment of thyroid nodules; treatment strategies by histological type (papillary carcinoma, follicular tumors, medullary carcinoma, poorly differentiated carcinoma, anaplastic carcinoma); radioactive iodine (RAI) therapy; management of advanced differentiated thyroid cancer; pharmacological treatment of thyroid cancer; and complications and safety management associated with thyroid surgery. For each category, "Clinical questions" (CQs) were established and the literature was searched, reviewed, extracted, selected, and examined.

Based on the available evidence and clinical expertise, the committee evaluated and determined the certainty of the evidence and the levels of recommendations. This

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Abbreviations: AE, adverse event; AFTN, auto-functioning thyroid nodule; AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control; ATA, American Thyroid Association; ATC, anaplastic thyroid carcinoma; BM, bone metastasis; BMA, bone-modifying agent; BSC, best supportive care; CDx, companion diagnostics; CEA, carcinoembryonic antigen; CGP, comprehensive genome profiling; CI, confidence interval; CQ, clinical question; CR, complete response; CSS, cause-specific survival; CT, computed tomography; DFS, disease-free survival; DT, doubling time; DTC, differentiated thyroid carcinoma; DM, distant metastasis; EBM, evidence-based medicine; FDG, fluorodeoxyglucose; FNAC, fine needle aspiration cytology; FT3, free-triiodothyronine; FT4, free-thyroxine; FTC, follicular thyroid carcinoma; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; HRQOL, health-related quality

of life; IONM, intraoperative neuromonitoring; JAES, Japan Association of Endocrine Surgery; LT4, levothyroxine; MEN, multiple endocrine neoplasia; MKI, multi-targeted kinase inhibitor; MRI, magnetic resonance imaging; NGS, next-generation sequencer; NLR, neutrophil/lymphocyte ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PD, progressive disease; PDTC, poorly differentiated thyroid carcinoma; PPS, parapharyngeal space; PR, partial response; PTC, papillary thyroid carcinoma; QOL, quality of life; RAI, radioactive iodine; RCT, randomized controlled trial; rhTSH, recombinant human thyroid-stimulating hormone; RLN, recurrent laryngeal nerve; SD, stable disease; SKI, selective kinase inhibitor; SRE, skeletal-related event; SM, spinal metastasis; Tg, thyroglobulin; TgAb, thyroglobulin antibody; Tg-DR, thyroglobulin doubling rate; Tg-DT, thyroglobulin doubling time; THW, thyroid hormone withdrawal; TKI, tyrosine kinase inhibitor; TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; TV-DR, tumor volume doubling rate; TV-DT, tumor volume doubling time; UMD, upper mediastinal dissection; US, ultrasound; VEGF-R, vascular endothelial growth factor receptor

was used to illustrate the overall clinical flow in a “Clinical algorithm”. When multiple treatment options are listed within a single column of the algorithm, those listed higher in the column are prioritized.

To aid in understanding the recommendations, background knowledge of the disease and established clinical procedures are provided in “Notes”. For recent insights or information where evidence is insufficient but considered clinically useful, “Columns” are used to present such information based on current evidence. Challenges for future revisions are outlined under “Future research questions”.

1) Setting CQs

A total of 32 CQs were selected. Both beneficial outcomes and adverse outcomes were considered in the extraction of outcomes.

2) Comprehensive literature search

The literature search was conducted by the Japan Medical Library Association, covering publications from January 1, 2010, to May 31, 2022. The search databases used were PubMed, Ichushi-Web, and The Cochrane Library. Literature published after June 2022 was also searched and extracted as necessary following the initial search process.

3) Systematic review

The systematic review team conducted all systematic reviews in a distributed manner. For each CQ, 2–3 members independently performed the initial screening to select studies that would proceed to the secondary screening based on titles and abstracts. The selection criteria for studies prioritized research designs in the following order: systematic reviews (including meta-analyses), randomized controlled trials, prospective observational studies, retrospective observational studies, and case reports. Additionally, the research content was evaluated for its relevance to the PICO (Population, Intervention, Comparison, Outcome) of the respective CQ. During the secondary screening, the full texts of selected papers were reviewed, and a table summarizing the research design, PICO, limitations, and risk of bias was created.

4) Evaluation of evidence

The internal and external validity of the evidence were assessed in light of knowledge on the clinical epidemiology. Key points of the evaluation are described in the “Summary and discussion of the literature” for each CQ. The “Certainty of evidence” was evaluated using the criteria outlined in Table 1.

5) Recommendations and their determination

For CQs concerning medical interventions (treatment), the format was “Is [specific treatment] recommended?” and a “Recommendation statement” was provided as an answer. In addition, the “Outcomes considered” (including both intended benefits and potential harms) were listed, the corresponding “Evidence” was presented, the “Summary and discussion of the literature” was provided, and the relevant references were included.

The “Strength of recommendation” was categorized as either “Strong” or “Weak”. The determination of the strength of the recommendation was based on the strength of evidence, but also involved extensive discussion of clinical usefulness, clinical applicability, and adverse events. This was decided through voting using the GRADE grid consensus form at the guideline development committee meeting [1]. For recommendations with a consensus rate $\leq 60\%$, key points of discussion were included in the explanatory text. Committee members with deep involvement in clinical trials directly related to the CQs or with financial conflicts of interest related to the manufacture or sale of relevant drugs or medical devices (economic conflicts of interest) abstained from voting in the recommendation decision meeting.

6) Evaluation of the guideline

After drafting, the final version of the guideline was reviewed by three external experts. The points raised during this review were examined by the guideline development committee, and necessary revisions and additions were made as needed.

7) Independence of the development process

The costs associated with guideline development (including literature search expenses, meeting costs, and transportation expenses for meeting participants) were

Table 1 Certainty (Strength) of evidence

A (High)	Strong confidence in the appropriateness of the estimated effect supporting the recommendation. This typically includes multiple high-quality randomized controlled trials or very reliable observational studies.
B (Moderate)	Moderate confidence in the appropriateness of the estimated effect supporting the recommendation. This generally includes randomized controlled trials with limitations or multiple consistent observational studies.
C (Low)	Limited confidence in the appropriateness of the estimated effect supporting the recommendation. This usually includes only observational studies or case series.
D (Very Low)	Little confidence in the appropriateness of the estimated effect supporting the recommendation. This often includes evidence with inconsistencies or a lack of high-quality evidence.

covered by the JAES. However, the guideline development committee worked independently to create the guideline, without intervention from the society.

Chapter 1. Overview of the diagnosis and treatment of thyroid nodules

Clinical algorithm 1-1. Basic diagnostic procedure for thyroid nodules (Fig. 1)

Clinical algorithm 1-2. Indications for fine-needle aspiration cytology (FNAC) of thyroid nodules (Fig. 2)

Clinical algorithm 1-3. Surgical indications for thyroid nodules diagnosed as benign (Fig. 3)

CQ 1-1.

Is thyroid cancer screening with ultrasound recom-

mended for asymptomatic adults without a family history or neck radiation exposure?

Recommendation statement

It is recommended that thyroid cancer screening with ultrasound be avoided for asymptomatic adults without significant thyroid cancer risk factors, such as a family history of thyroid cancer or related genetic syndromes, or a history of neck radiation exposure during childhood.

Certainty of evidence: B

Strength of recommendation: Weak; **Consensus rate:** 78%

Outcomes considered

- Thyroid cancer mortality rate
- Thyroid cancer incidence rate
- Stage and treatment prognosis at the time of thyroid cancer surgery
- Adverse events from thyroid cancer screening
- Patient-reported outcomes

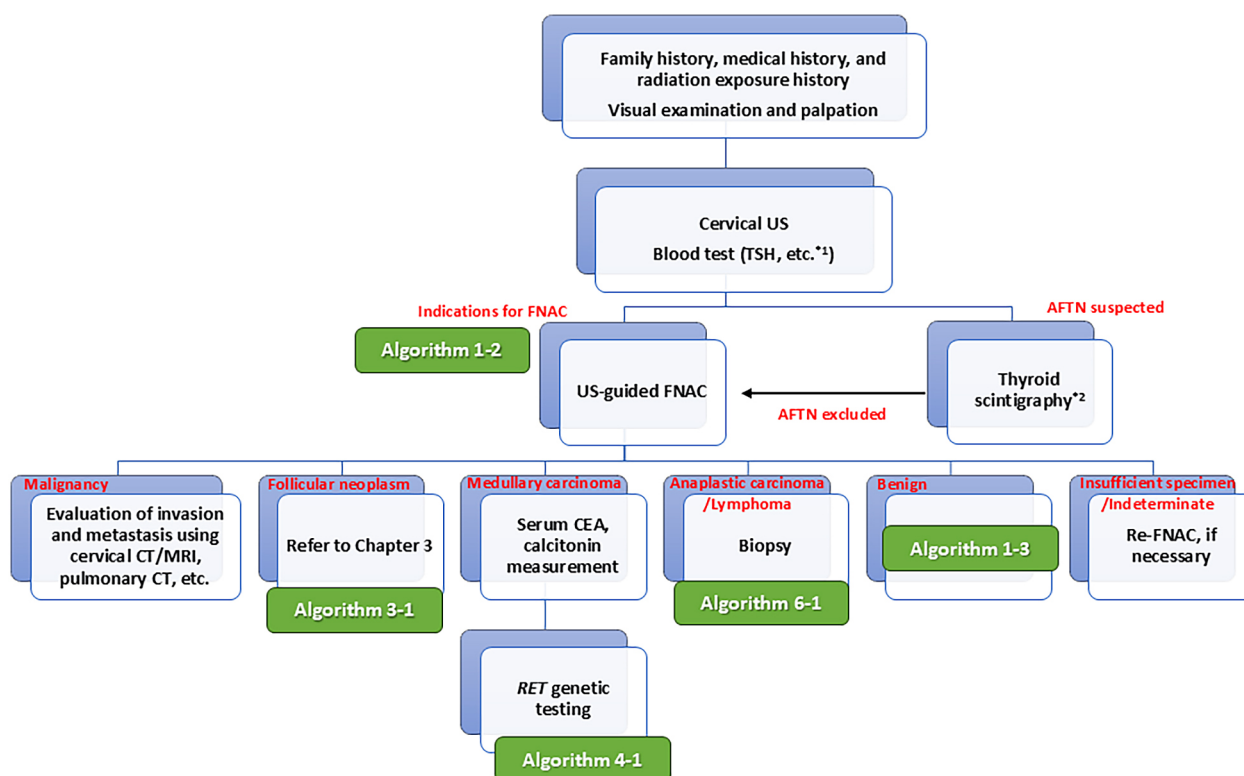


Fig. 1 Clinical algorithm 1-1. Basic diagnostic procedure for thyroid nodules

*1 In addition to measurement of TSH, measurement of free-T4, free-T3, thyroglobulin (Tg), Tg antibody, and thyroid peroxidase antibody is recommended.

*2 ^{123}I scintigraphy (or $^{99\text{m}}\text{Tc}$ scintigraphy): Except when suspecting AFTN, there is no indication for various scintigraphies (including FDG-PET) to determine the benign or malignant nature of a nodule.

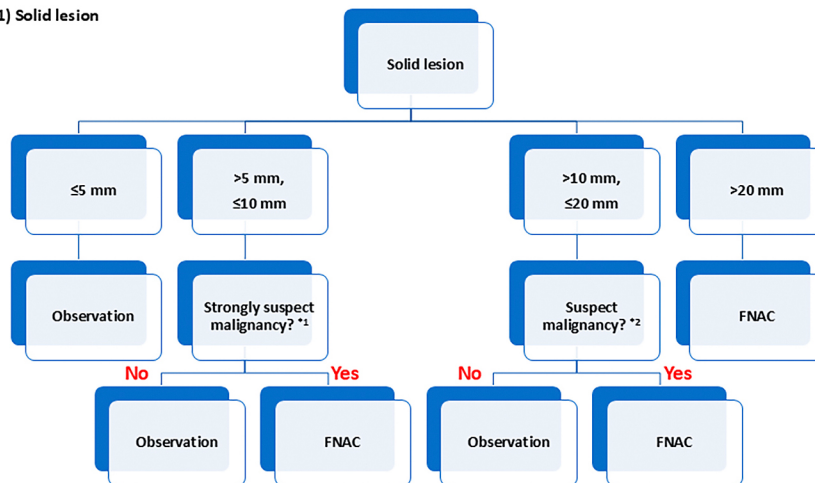
CT and MRI also do not contribute to determining benign or malignant status.

US: ultrasound; TSH: thyroid-stimulating hormone; FNAC: fine-needle aspiration cytology; AFTN: auto-functioning thyroid nodule; CT: computed tomography; MRI: magnetic resonance imaging; CEA: carcinoembryonic antigen; FDG-PET: fluorodeoxyglucose-positron emission tomography.

Evidence

- No prospective studies have directly compared outcomes between asymptomatic adults with and without screening.
- Autopsies performed on individuals who died from causes other than thyroid cancer have revealed small PTCs in about 10% of cases, and this frequency has not changed since the 1970s.
- Since the 1980s, the incidence of small PTCs has increased globally, while the thyroid cancer mortality rate has shown little change.
- A positive correlation exists between the rate of

1) Solid lesion



2) Cystic lesion

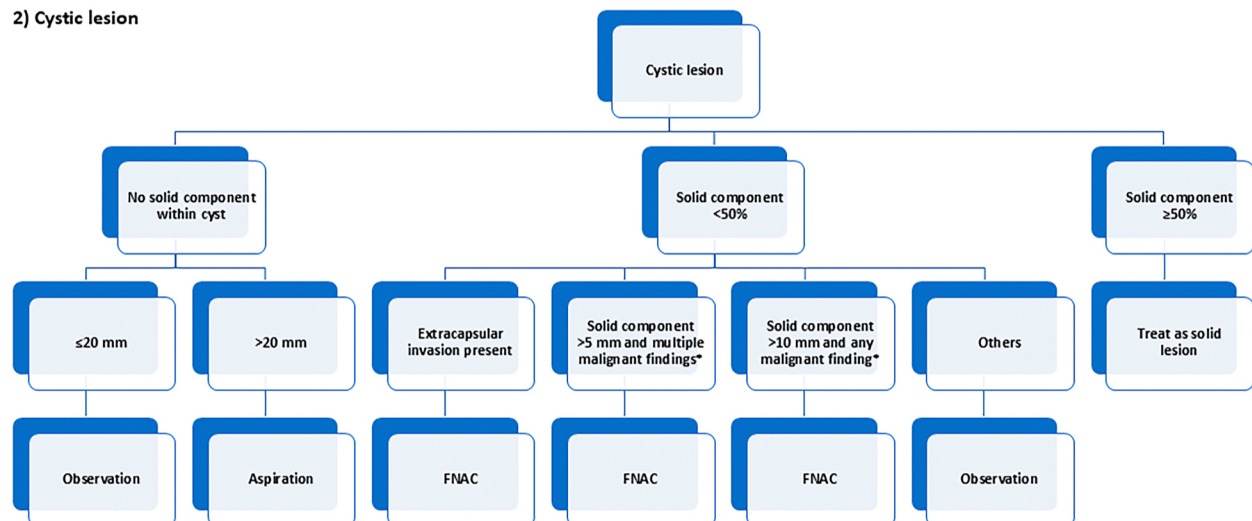


Fig. 2 Clinical algorithm 1-2. Indications for fine-needle aspiration cytology (FNAC) of thyroid nodules

- Pay attention not only to tumor size and ultrasound findings, but also to the presence of cervical lymph node enlargement or extrathyroidal extension. Perform FNAC when these conditions are observed.
- For lymph node enlargement, measuring Tg in the aspirated washout (or measuring calcitonin if medullary thyroid carcinoma is suspected) can be useful for diagnosing metastasis.
- Perform FNAC if distant metastasis is suspected.
- Perform FNAC if blood tests show elevated CEA or calcitonin levels and medullary thyroid carcinoma is suspected.
- Even if the nodule appears to be a typical adenomatous nodule, perform FNAC if nodule diameter exceeds 20 mm.
- Avoid FNAC if parathyroid enlargement is suspected.

1) Solid lesion

Malignant findings: irregular shape, indistinct or coarse margins, low internal echogenicity, heterogeneous internal echogenicity, multiple tiny areas of high echogenicity, irregular or absent low-echogenicity halo at the margin

*1: If almost all items apply

*2: If any of the findings apply, or if intranodular blood flow is observed on Doppler imaging

2) Cystic lesion

*Malignant findings: irregular shape of solid component, multiple fine areas of high echogenicity, increased blood flow

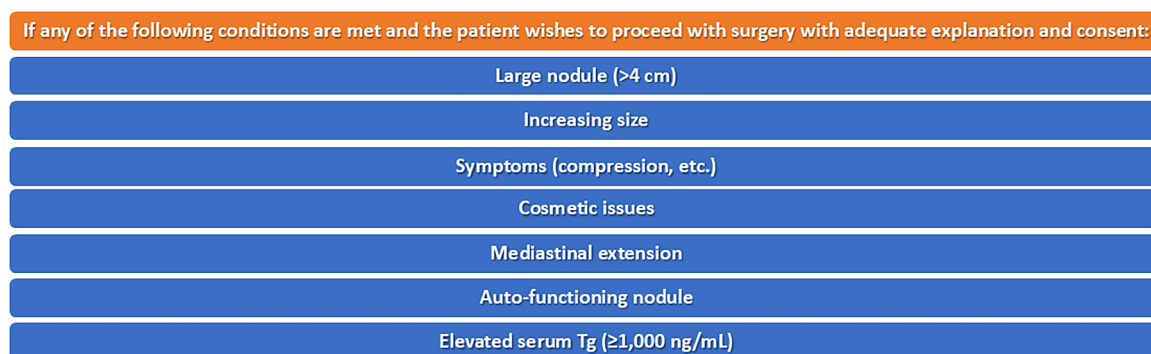


Fig. 3 Clinical algorithm 1-3. Surgical indications for thyroid nodules diagnosed as benign

For surgical indications in cases diagnosed as “follicular neoplasm,” refer to CQ3-1.

Even if FNAC indicates a benign nodule, there is a 2–7% chance that the nodule will be diagnosed as malignant on pathological examination.

ultrasound screening and the detection rate of PTC.

- Serious adverse events from thyroid cancer ultrasound screening or ultrasound-guided FNAC are rarely reported.
- Thyroid cancer treatment can result in adverse events such as hypothyroidism, hypoparathyroidism, and recurrent laryngeal nerve paralysis, with the frequency varying depending on the aggressiveness of treatment.

Summary and discussion of the literature

1) Rising incidence of papillary thyroid carcinoma (PTC) and its causes

Recently, an increase in the incidence of thyroid cancer has been reported worldwide, with most of this increase attributed to PTC, particularly small tumors less than 2 cm in diameter. In contrast, few reports have described changes in mortality rates for thyroid cancers. The increased incidence is mainly attributed to the widespread adoption of high-resolution imaging techniques such as ultrasound, and increased opportunities for screening [2-4].

Latent PTC (*i.e.*, cancer that shows no clinical signs during life but is first detected postmortem) has long been recognized as highly prevalent in the thyroid. According to a meta-analysis of 35 studies from 1949 to 2007, the prevalence of latent PTC found at autopsy in 12,834 individuals who died from causes other than thyroid cancer was 11.2%, and this rate has basically remained unchanged since 1970 [5]. The recent increase in PTC cases is interpreted as reflecting the increased detection of small, indolent cancers that would have otherwise remained unnoticed throughout the lifetime of the patient, thanks to the advent of simple and increasingly accurate diagnostic tests. Indeed, a positive correlation has been reported between the rate of thyroid ultrasound screenings and the incidence of thyroid cancer [6-9]. However, most cases are less than 2 cm in maximum

diameter and remain confined to the thyroid or regional lymph nodes without distant metastases [10].

2) Frequency and the effect of thyroid cancer detection

According to a report by Takebe *et al.* in 1994, thyroid ultrasound screening performed alongside breast cancer screening and fine needle aspiration cytology (FNAC) for nodules larger than 3 mm led to the detection of PTC in 3.5% of participants [11]. In South Korea, since 1999, the widespread implementation of thyroid cancer screening using ultrasound has resulted in a 15-fold increase in the incidence of PTC by 2011 compared to 1993. However, most of these cancers were smaller than 1 cm, and no change in mortality rates was seen [12]. Recent research using a multi-center database from South Korea found that the odds ratio of thyroid cancer death for individuals who did not undergo screening compared to those who did was 1.13 (95% confidence interval [CI]: 0.49–2.63), indicating no association between screening and prevention of thyroid cancer deaths [13].

A large-scale database study in China estimated that between 2019 and 2030, thyroid cancer would be identified in 1 million 20- to 64-year-old individuals if screening were not conducted, compared to 11.4 million cases if screening were to be performed [14]. In addition, a simulation study analyzing the cost-effectiveness of thyroid cancer screening with ultrasound among asymptomatic adults in the United States found that quality-adjusted life years for the group that underwent screening was 18.74 years, compared to 18.71 years for the group with clinically detected cancer, showing no significant difference. Cumulative medical costs were \$18,819 for the screening group, compared to \$15,864 for the non-screening group, leading to the conclusion that ultrasound screening is not sufficiently cost-effective [15].

3) Direct harms of thyroid cancer screening and treatment

Serious adverse events from thyroid cancer screening with ultrasound have not been reported. Although bleeding or tumor dissemination have been reported following FNAC, such events are clearly infrequent [16, 17]. In thyroid cancer treatment, adverse events such as hypothyroidism, hypoparathyroidism, and recurrent laryngeal nerve paralysis occur at certain frequencies depending on the extent of thyroidectomy, lymph node dissection, and the presence and degree of adjuvant therapy [3]. No direct, prospective studies have compared the risk of thyroid cancer death, treatment outcomes, or patient-reported outcomes between those who undergo screening and those who do not. However, a study comparing immediate surgery (974 cases) and active surveillance (1,179 cases, with 94 later undergoing surgery) for very low-risk PTCs showed no difference in neck recurrence or overall mortality. Transient vocal cord paralysis, transient and permanent hypoparathyroidism, thyroid hormone replacement, and postoperative bleeding were found to be significantly more common in the immediate surgery group [18].

Based on the above, there is insufficient evidence that ultrasound screening for thyroid cancer in asymptomatic adults without specific risk factors, such as family history, hereditary syndromes related to thyroid cancer, or childhood neck radiation, contributes to any reduction in overall thyroid cancer mortality rate or improves the health status of screened individuals. Such screening is therefore not recommended. The screening effect increases the incidence of PTC, and there is a risk of increasing the number of cancer survivors who experience physical, psychological, and economic burdens due to surgery, adjuvant therapy, or surveillance. This conclusion is consistent with the statement by the U.S. Preventive Services Task Force [19].

CQ 1-2.

Is immediate surgery recommended for a diagnosis of PTC during pregnancy?

Recommendation statement

Immediate surgery is not recommended for PTC diagnosed during pregnancy.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 78% (re-vote)

Outcomes considered

- Disease stage at surgery
- Treatment prognosis
- Impact on the fetus (miscarriage rate, incidence of congenital abnormalities)
- Adverse events related to surgery and anesthesia
- Patient-reported outcomes

Evidence

- All studies comparing the prognosis and prognostic factors of PTC diagnosed during pregnancy with those diagnosed outside of pregnancy were retrospective studies. Some studies suggested higher rates of recurrence in pregnancy-related cases, but many reported no difference in stage or prognosis.
- Research comparing the timing of surgery during pregnancy *versus* after delivery was limited to small-scale retrospective studies. No reports showed differences in disease-specific or overall survival, and no differences in stage or recurrence rates were reported.
- No reports have indicated that surgery or anesthesia during the second trimester of pregnancy increases the risk of adverse events, miscarriage, or congenital abnormalities.
- No research reports have provided patient-reported outcomes.

Summary and discussion of the literature

1) Impact of pregnancy on progression of PTC

Reports suggest that rates of recurrence may be higher in cases of differentiated thyroid carcinoma diagnosed during pregnancy compared to those diagnosed outside of pregnancy [20]. but the pathophysiological mechanisms underlying such differences remain unclear. A study using the California Cancer Registry compared 301 women with differentiated carcinoma who were recently pregnant to 903 age- and race-matched women who were not pregnant. The study found no differences in tumor size, extrathyroidal extension, lymph node metastasis, distant metastasis, stage, or 5-year disease-specific survival. Multivariate analysis also indicated that recent pregnancy was not associated with tumor size, extrathyroidal extension, lymph node metastasis, or distant metastasis [21]. In addition, pregnancy is not considered a significant risk factor for progression in cases of very low-risk PTC under active surveillance [22, 23] or in patients with lung metastases of PTC after RAI therapy [24].

2) Timing of surgery

Regarding the timing of surgery for cases diagnosed with PTC during pregnancy, no impact on survival rates was seen according to whether the surgery was performed during pregnancy or deferred until after delivery [25]. Uruno *et al.* compared 24 cases of PTC operated on during pregnancy (19 in the second trimester) with 21 cases operated on within 1 year postpartum. No significant differences between groups were found in surgical complications, anesthesia-related adverse events, miscarriages, or congenital abnormalities. Age and stage were also similar between groups. Local recurrences were noted in three cases from the pregnancy surgery group and one case from the postpartum surgery group, but no

difference was found in recurrence-free survival rates [26].

Since PTCs typically grow slowly, delaying surgery until after delivery does not change the prognosis, except in cases where the patient strongly desires early surgery or clear progression is evident by the second trimester. Pregnancy thus does not need to be interrupted solely due to the diagnosis of PTC. If performed during pregnancy, surgery should be undertaken in the second trimester to minimize adverse effects on both the mother and fetus (*e.g.*, organ formation changes and miscarriage in early pregnancy; preterm birth and stillbirth in late pregnancy). The surgery should be performed by an experienced surgeon, and postoperatively, attention should be given to maternal thyroid and parathyroid functions.

If surgery is deferred, no evidence supports the usefulness of thyroid-stimulating hormone (TSH) suppression therapy during pregnancy.

Based on the above, pregnancy does not need to be interrupted if PTC is diagnosed during pregnancy. Postpartum surgery does not change the prognosis, but if the patient strongly desires surgery or rapid progression is identified, performing the surgery during the second trimester of pregnancy would be preferable.

Chapter 2. Papillary thyroid carcinoma (PTC)

Note 2-1. Prognostic factors and risk classification of PTC

In the “Clinical Practice Guidelines for Thyroid Tumors 2018”, PTC was divided into four risk classifications based on tumor size, lymph node metastasis, extension from primary lesions and metastatic lymph nodes, and distant metastasis: very low; low; intermediate; and high [27]. Ito *et al.* then published a report verifying the appropriateness of this risk classification, showing that

cause-specific survival, distant organ recurrence-free survival, and local recurrence-free survival all worsened in increasing order of very low/low, intermediate, and high-risk cases [28, 29]. Since that clearly proved the appropriateness of the risk classification, the present guideline adopts the same risk classification (Table 2).

However, this risk classification does not consider age, which is a very strong prognostic factor. In 2020, Ito *et al.* performed subset analyses in patients ≥ 55 or < 55 years old [30]. The prognosis of very low/low-risk patients was found to be very favorable regardless of age (20-year cause-specific survival rate, 99.8%). Conversely, prognoses of high-risk cases differed significantly according to patient age, with a 20-year cause-specific survival rate of 80.6% in high-risk cases ≥ 55 years old, significantly lower than that in patients < 55 years, at 96.6% ($p < 0.0001$). No significant difference was detected between the prognoses of high-risk patients < 55 years and intermediate-risk patients ≥ 55 years old.

Table 3 summarizes the prognosis of PTC patients according to risk classification in four representative Japanese institutions. While biases would be present among these institutions, but all institutions showed particularly poor cause-specific and distant recurrence-free survivals in high-risk patients ≥ 55 years old. A significant difference in the prognosis of intermediate-risk patients is seen according to patient age, but this difference is small. Further, prognosis did not differ significantly between high-risk patients < 55 years old and intermediate-risk patients. Taking these together, the relationship between risk classification and prognosis is shown in Table 2. Physicians should decide surgical designs and whether adjuvant therapies should be administered after understanding the prognosis in each case.

Column 2-1. Molecular prognostic factors of PTC

The first molecular prognostic factor for PTC to attract

Table 2 Risk classifications and prognoses of PTC patients

Risk classification in the present guidelines	Clinical features of each risk group	Carcinoma death/distant recurrence rates
Very low risk	T1aN0M0	Carcinoma death rate: 0–2% Distant recurrence rate: 1–2%
Low risk	T1bN0M0	
Intermediate risk	Cases not classified as very low, low, or high risk	Carcinoma death rate: 0–2% Distant recurrence rate: 2–27%
High risk, young patient (< 55 years)	1) T > 4 cm 2) $\geq$ Ex2a 3) N1a-2 or N1b-2 (maximal N diameter > 3 cm, or presence of extranodal tumor extension)	
High risk, old patient (≥ 55 years)	4) M1 Cases fulfilling ≥ 1 factor	Carcinoma death rate: 18–46% Distant recurrence rate: 24–48%

Table 3 Survival rates of PTC patients according to risk classification in four Japanese representative institutions

Risk classification	20-year cause-specific survival rate (%)				20-year distant recurrence-free survival rate (%)			
	Kuma Hospital	CIH/NMS ¹⁾	Ito Hospital	TWMU ²⁾	Kuma Hospital	CIH/NMU	Ito Hospital	TWMU
Very low/low	99.8	98.8	99.3	98.4	99.4	99.1	97.8	99.1
Intermediate <55 years	97.7	100	100	97.1	98.2	92.3	83.7	94.9
Intermediate ≥55 years	96.9	97.1	93.9	92.9	95.6	94.2	73.1	78.6
High <55 years	96.6	92.1	98.2	97.3	91.8	85.4	93.4	87.8
High ≥55 years	80.6	54.0	82.4	60.9	55.9	55.9	66.6	51.5

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2) Tokyo Women's Medical University

attention was *BRAF* mutations. With these mutations, MEK located downstream of the MAPK pathway is always activated, resulting in the promotion of cell growth. The most common point mutation is V600E, and the incidence of PTC reported in previous studies has ranged from 30% to 80%; rates differed considerably between reports but were generally high. From the early 2000s to the 2010s, many reports from Western countries and Korea demonstrated that cases with *BRAF* mutations showed poorer prognosis. However, according to reports from Japan, *BRAF* mutations do not affect prognosis in PTC patients [31, 32]. Differences in pathological diagnosis and race were regarded as possible reasons for these discrepancies, but at least in Japan, *BRAF* mutations cannot be concluded to represent strong prognostic factors for PTC.

At present, the most useful molecular prognostic marker for PTC is *TERT* promoter mutation, which is considered to increase the amount of *TERT* transcription. In 2014, Xing *et al.* showed that the recurrence rate of PTC displaying both *BRAF* V600E and *TERT* C228T mutations was significantly poorer than that of others [33]. Another report from Japan showed that *TERT* promoter gene mutation was an independent prognostic factor for disease-free and cause-specific survivals in PTC patients [34]. Further, Matsuse *et al.* demonstrated that classifying PTC into three groups in combination with *TERT* promoter/*BRAF* gene mutations and Ki-67 labeling index was useful for predicting PTC recurrence [32]. Many reports from other countries have been published and a few meta-analyses have also been published, concluding that *TERT* promoter mutation offered a strong prognostic factor [35, 36]. In addition, some studies have shown a relationship between *TERT* promoter mutation and RAI-refractory metastasis [37] and have demon-

strated that PTC patients with *TERT* hyperexpression show dire disease-free survival even in the absence of *TERT* promoter mutation [38].

Some studies have been published regarding *TERT* promoter mutation in papillary thyroid microcarcinoma. Yabuta *et al.* investigated *BRAF* gene and *TERT* promoter mutations in 10 patients who underwent conversion surgery after active surveillance because of tumor enlargement, 5 patients who underwent surgery due to the appearance of lymph node metastases, and 11 patients who underwent surgery despite no progression [39]. They reported that although *BRAF* mutation was detected in 64–80%, none of these cases showed *TERT* promoter mutation [39]. In studies from other countries, the incidence of *TERT* promoter mutation in papillary thyroid microcarcinoma was reported as very low, at 3.2% and 4.7%, and was unrelated to prognosis [40, 41]. The presence or absence of *TERT* promoter mutation is thus not considered useful in deciding surgical indications for papillary thyroid microcarcinoma.

Other gene mutations include fusion genes such as *RET/PTC* and *RAS* mutation, but no relationships between these and prognosis have been reported.

Clinical algorithm 2-1. Initial treatments and postoperative monitoring for PTC based on risk classification system (Fig. 4)

CQ 2-1.

Is active surveillance recommended for adult very low-risk PTC?

Recommendation statement

Active surveillance is recommended for adult very low-risk PTC.

Certainty of evidence: B

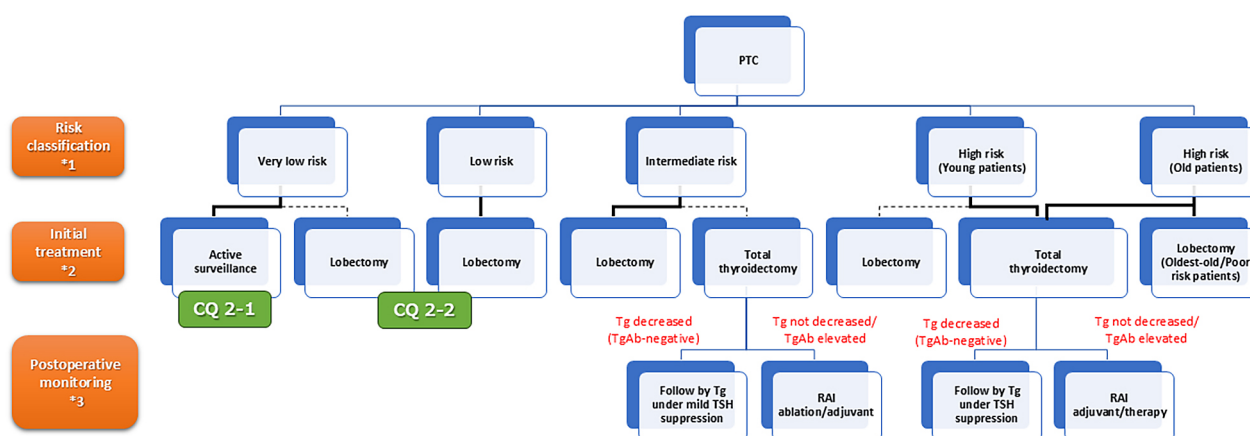


Fig. 4 Clinical algorithm 2-1. Initial treatments and postoperative monitoring for papillary thyroid carcinoma (PTC) based on risk classification system

*1 See Note 2-1.

*2 Based on preoperative evaluation, therapeutic neck dissection is added. Prophylactic dissection of the lateral compartment is not recommended (see CQ2-3).

*3 See Notes 2-3, 2-4, and 2-5. For postoperative follow-up, add imaging studies such as ultrasound examination as appropriate.

Tg: thyroglobulin; TgAb: thyroglobulin antibody; TSH: thyroid-stimulating hormone; RAI: radioactive iodine.

Strength of recommendation: Strong; **Consensus rate:** 89%

Outcomes considered

- Tumor progression rate
- Prognosis
- Adverse events
- Medical costs
- Health status from the patient's perspective

Evidence

- The progression rate of adult very low-risk PTC is very low under active surveillance, and life-threatening recurrence was very rare even after surgery at the time of slight progression.
- Unlike clinical PTC, young patients were more likely to show progression, but postoperative prognosis after conversion surgery remained excellent.
- The prognosis of patients who underwent immediate surgery did not differ from that of those who received active surveillance (including those who underwent conversion surgery because of carcinoma progression).
- The incidence of adverse events from immediate surgery was significantly higher than that with active surveillance. Further, the incidence of adverse events did not differ between patients who underwent immediate surgery and those who received conversion surgery after active surveillance.
- Physical quality of life (QOL) was more often reported as better in patients who underwent active surveillance than in patients who received immediate surgery.

Summary and discussion of the literature

A systematic review of active surveillance for very

low-risk PTC was performed by the Japan Thyroid Association and published in 2021 as a position paper [4]. Also, regarding concrete indications and implementation, consensus statements have been published from the Japan Association of Endocrine Surgery [42].

1) Outcomes for patients with active surveillance

Table 4 indicates the results of prominent prospective studies. Incidences of enlargement and the appearance of node metastasis were generally low [43-50], with no patients dying of thyroid carcinoma during active surveillance or after conversion surgery for carcinoma progression. Tuttle *et al.* reported that one of 483 PTCs measuring ≤ 1.5 cm showed rapid enlargement (tumor volume doubling time (TV-DT), 0.7 years) despite appearing initially stable. Postoperatively, *BRAF* mutation-positive oncocytic PTC with poorly differentiated components was diagnosed [46]. Miyauchi *et al.* also found that one of 3,222 patients who underwent active surveillance showed lung metastasis after conversion surgery undertaken at the insistence of the patient [51]. Further, they reported that one of the 2,424 patients who underwent immediate surgery showed postoperative lung recurrence.

2) Risk of progression and evaluation of tumor enlargement

Previous studies have shown that the incidence of progression (tumor enlargement or appearance of node metastasis) for very low-risk PTC during active surveillance is higher in young patients [43-45, 47]. However, Miyauchi *et al.* estimated the life-time probability of progression for patients in their 20s remained at 48.6% [52].

Table 4 Prospective studies of active surveillance for low-risk PTC

Authors	Institution, Country	Number of cases	Active surveillance period	Definition of progression	Enlargement rate	Node metastasis appearance rate	Predictive factors for enlargement	Predictive factors for node metastasis appearance
Ito <i>et al.</i> 2023 [43]	Kuma Hospital, Japan	2705	1–157 years (median 5.5 years)	Maximal diameter increase by ≥3 mm	3.0% for 5 years, 5.5% for 10 years, and 6.2% for 15 years	0.9% for 5 years, 1.1% for 10 years and 15 years	Age <40 years, high TSH level, tumor size ≥9 mm	Age <40 years, male sex
Lee <i>et al.</i> 2022 [44]	Multicenter study, South Korea	755	Median 41.4 months	Increase by ≥3 mm in one direction, by ≥2 mm in two directions, novel appearance of extrathyroidal extension and lymph node metastasis	2- and 5-year enlargement rate 5.3%, 14.2%, respectively	0%	Age <30 years, male sex, tumor size ≥6 mm	Not described
Nagaoka <i>et al.</i> 2021 [45]	Nippon Medical School, Japan	571	1–26 years (average, 7.6 years)	Maximal diameter increase by ≥3 mm	4.3% for 5 years, 9.9% for 10 years, 25.2% for 20 years	1.4% for 10 years, 3.9% for 20 years	Age <40 years (analyzed tumor enlargement and node metastasis appearance as a single group)	
Tuttle <i>et al.</i> 2022 [46]	Sloan Kettering Memorial Cancer Center, USA	483	0.5–17 years (median, 3.7 years)	Tumor volume increase by ≥72%, maximal diameter increase by ≥3 mm, >24%	TV >72% increase in 59 cases (12%), maximal diameter increase by >3 mm (9%), maximal diameter increase by >24% in 64 patients (13%). 5-year TV >72% enlargement rate, 15.9%. One showed rapid enlargement after being stable for >5 years (pathology, oncocytic poorly differentiated PTC)	Appearance of node metastasis in 7 (1.4%), 5-year node appearance rate 1.5%.	Not described	Not described

Table 4 Cont.

Authors	Institution, Country	Number of cases	Active surveillance period	Definition of progression	Enlargement rate	Node metastasis appearance rate	Predictive factors for enlargement	Predictive factors for node metastasis appearance
Oh <i>et al.</i> 2018 [47]	Multicenter study, South Korea	370	23.6–47.0 months (median 34.1 months)	1. maximal diameter increased by ≥ 3 mm; 2. volume increased by $\geq 50\%$	1. 3.2% for 3 years, 6.4% for 5 years 2. 17.3% for 3 years, 36.2% for 5 years	8.6%	Age <45 years	Not described
Sanabria 2020 [48]	Universidad de Antioquia, Colombia	102 (Low-risk PTC ≤ 1.5 cm)	0.2–112 months (median, 13.9 years)	1. maximal diameter increased by ≥ 3 mm 2. volume increase by $\geq 50\%$	1. 10.2% for 2 years 2. 23% for 2 years	0%	Not described	Not described
Molinaro <i>et al.</i> 2020 [49]	University Hospital of Pisa, Italy	93 (Low-risk PTC ≤ 1.3 cm)	6–54 months (median, 19 months)	1. maximal diameter increased by ≥ 3 mm 2. volume increased by $\geq 50\%$	1. 2.2% 2. 16%	1.1%	Not described	Not described
Rosario <i>et al.</i> 2019 [50]	Ensino e Pesquisa da Santa Casa de Belo Horizonte, Brazil	70 (Low-risk PTC ≤ 1.2 cm, age ≥ 20 years)	18 patients with 6 examinations twice per year, 24 with ≥ 5 times, 36 with ≥ 4 times, 45 with ≥ 3 times, and 70 with ≥ 1 time	1. maximal diameter increase by ≥ 3 mm 2. volume increased by $\geq 50\%$ Novel appearance of extrathyroidal extension and lymph node metastasis	One case progressed after 30 months (extrathyroidal extension appeared) 3 showed decrease in TV $\geq 50\%$.	0%	Not described	Not described

Further, Ito *et al.* showed that the growth activity of very low-risk PTC after enlargement was significantly decreased compared with before enlargement [53]. The progression activity of very low-risk PTC is indicated to frequently decrease with patient age and time, so undertaking conversion surgery immediately after identifying slight tumor enlargement is considered premature. On the other hand, while the incidence of growth for very low-risk PTC in elderly patients is low, the lack of evidence regarding age and the period after which active surveillance can be ended means that lifetime active surveillance is basically required.

One report claimed that taking a 50% increase in tumor volume as representative of enlargement is useful for early detection of progressive cases [54]. However, in clinical practice, judging tumor enlargement based on a ≥ 3 -mm increase in maximal diameter offers a simpler threshold for initiating active surveillance, with less observer variation [42].

3) Prognoses of patients with immediate surgery and conversion surgery

A systematic review of 14 manuscripts on very low-risk PTC conducted by Chou *et al.* found no significant difference in disease-free or cause-specific survivals between an active surveillance group and an immediate surgery group [55]. Fujishima *et al.* reported that postoperative prognoses did not differ significantly between patients who underwent immediate surgery and those who received surgery after active surveillance for various reasons [56]. The same results were obtained by comparing an immediate surgery group and conversion surgery group after progression under active surveillance [56].

4) Adverse events

According to Oda *et al.*, even when experts performed surgery, two (0.2%) and 16 (1.6%) of 974 patients suffered intraoperative recurrent laryngeal nerve (RLN) injury and permanent hypoparathyroidism, respectively [18]. A subsequent study by Sasaki *et al.* compared 1,739 patients with immediate surgery and 242 patients with conversion surgery after active surveillance, reporting that the incidence of adverse events did not differ between groups [57].

5) Comparison of medical costs

A comparison of medical costs showed results varying according to countries, but a manuscript comparing medical costs between active surveillance and immediate surgery showed that 10-year medical costs for immediate surgery were 4.1-times higher than for active surveillance under the Japanese insurance system [58].

6) Influence on QOL

As shown in Table 5, six manuscripts have been published comparing the influence on health-related QOL between active surveillance and immediate surgery

[59–64]. Various biases exist in the study designs and QOL scales, but most reports concluded that physical QOL was superior in the active surveillance group compared to the immediate surgery group. Discrepant results were reported for mental QOL, possibly reflecting the influences of trait anxiety (original patient characteristic of readily feeling anxiety) and observation period.

CQ 2-2.

Is lobectomy recommended for low-risk PTC in only one lobe?

Recommendation statement

Lobectomy is recommended for low-risk PTC present in one lobe.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 89%

Outcomes considered

- Prognosis after treatment
- Surgical complications
- Health status from the patient's perspective

Evidence

- With low-risk PTC, recurrence rate did not depend on whether total thyroidectomy or lobectomy was performed, except for recurrence to the remnant thyroid.
- In patients without distant metastases and in those aged ≥ 50 years without obvious extrathyroidal extension or lymph node metastases ≥ 3 cm, whether total thyroidectomy or lobectomy was performed did not affect recurrence-free or cause-specific survivals.
- Regarding health status-related QOL, patients who underwent total thyroidectomy had more complaints than those who received lobectomy, but other reports found that complaints were unrelated to the extent of thyroidectomy and concerns about recurrence were stronger in patients who underwent lobectomy.

Summary and discussion of the literature

Table 6 summarizes reports regarding the relationship between extent of thyroidectomy and prognosis in patients with low-risk (or very low-risk) PTC. According to a report from Kuma Hospital in 2010 [65], disease-free survival in 1,037 T1N0M0 PTC who underwent total thyroidectomy was significantly better than that in 1,601 patients who received non-total thyroidectomy, but this was because 17 cases (1.1%) without total thyroidectomy showed recurrence to the remnant thyroid. If these 17 cases were excluded, prognosis would not have differed between groups. In this series, 4 showed distant recurrence and 2 patients died of thyroid carcinoma.

In 2010, Sugitani *et al.* developed the CIH (Cancer Institute Hospital) classification system to predict cancer-specific mortality due to PTC. The system defined high mortality risk group as patients with distant

Table 5 Patient-reported outcome studies comparing immediate surgery with active surveillance in very low-risk PTC

Cross-sectional studies				
Institution, Country, Year	Number of cases	Period from diagnosis to investigation	Tools for measuring QOL	Results
Asan Medical Center, Korea, 2019 [59]	Surgery 148 Active surveillance 43	Median, 38.0 months Median, 29.6 months	SF-12v2 THYCA-QOL FoP	Fewer mental problems in the active surveillance group. Trait anxiety and follow-up period are significant predictors of state anxiety, rather than management policy Problems about symptoms of nerves, muscles, pharynx, and mouth cavity and those involving the wound were fewer in the active surveillance group. No difference between groups was present regarding fear of carcinoma progression.
Tokyo Women's Medical University, Japan, 2020 [60]	Surgery 30 Active surveillance 20	Median 4.25 years Median 4.05 years	STAI VAS (a scale independently established for measuring symptoms and uneasiness)	Although the active surveillance group had stronger anxiety, this was related to the trait anxiety of individual patients rather than selection of management policy. Degree of anxiety was inversely related to follow-up period. Concerns regarding neck discomfort, weak voice, neck appearance were fewer in the active surveillance group.
Kuma Hospital, Japan, 2020 [61]	Surgery 49 Active surveillance 298	Median, 84 months Median, 56.5 months	THYCA-QOL HADS	Complaints regarding voice, psychological problems, operation scar, and increased body weight were fewer in the active surveillance group. Further, uneasiness and depression were significantly fewer in the active surveillance group.
Cancer Institute Hospital/Nippon Medical School [62]	Surgery 32 Active surveillance 249	Median, 4.0 years Median, 7.9 years	STAI SF-36v2 VAS (same as [23])	After propensity score matching, trait anxiety and mental health conditions were better in the active surveillance group. Neck symptoms were stronger in the surgery group. In the active surveillance group, state anxiety was significantly better in cases with light trait anxiety and long follow-up.
Longitudinal studies				
Institution, Country, Year	Number of cases	Period from diagnosis to investigation	Tools for measuring QOL	Results
Seoul National University Hospital, Seoul National University Bundang Hospital, National Cancer Center, Korea, 2019 [63]	Surgery 203 Active surveillance 192	Average, 7.1 ± 4.2 months Average, 9.3 ± 4.8 months	Thyroid-specific QOL questionnaire	Baseline psychological health and physical and psychological health at 8.2 months (average follow-up) were superior in the active surveillance group compared to the immediate surgery group.
Seoul National University Hospital, Seoul National University Bundang Hospital, National Cancer Center, Korea, 2021 [64]	Surgery 381 Active surveillance 672	Median, 24.6 months Median, 24.0 months	Thyroid-specific QOL questionnaire	After modulating age, sex, baseline tumor size and QOL score, the 2-year QOL scores were good in descending order of the active surveillance group, lobectomy group and total thyroidectomy group. In patients who underwent conversion surgery after active surveillance, QOL was better in patients who underwent conversion surgery because of tumor progression than in those for whom PTC did not progress.

SF-12v2: 12-item short-form health survey variation 2.0; SF-36v2: 36-item short-form health survey version 2.0; THYCA-WOL: thyroid cancer-specific health-related quality of life questionnaire; FoP: Fear of Progression questionnaire; STAI: State-Trait Anxiety Inventory; VAS: visual analog scale; HADS: Hospital Anxiety and Depression Scale.

Table 6 Comparative studies of the extent of thyroidectomy and prognosis in low-risk PTC

Authors	Patients	Follow-up	Surgical design	Outcomes	Results
Ito <i>et al.</i> [65]	cT1N0M0 TPC 2,631 patients	Average, 91 months	Total/near-total 1,037 patients Lobectomy 1,601 patients	DFS rates	Total/near-total group showed better DFS ($p = 0.0172$), but no significant difference after excluding recurrence in remnant thyroid
Sugitani <i>et al.</i> [66]	CIH low-risk 498 patients	Not described	Total/near-total 47 patients Non-total 451 patients	DFS rate and CSS rate	No significant difference
Ebina <i>et al.</i> [67]	CIH low-risk 967 patients (except for PTMC)	Average, 8.3 years	Total/near-total 176 patients Non-total 791 patients	DFS rate and CSS rate	No significant difference
Kim <i>et al.</i> [68]	cT1aN0M0 8,676 patients	Average, 64.6 months	Total/near-total 5,387 patients Lobectomy 3,289 patients	Local DFS rate	Total/near-total group showed better DFS ($p < 0.001$), but no significant difference after excluding recurrence in remnant thyroid
Kwon <i>et al.</i> [69]	cT1aN0M0 2,031 patients	Median, 8.5 years	Total/near-total and lobectomy 688 patients each after matching individual risk factors	Local DFS rate	Total group showed better DFS ($p = 0.01$), but no significant difference after excluding recurrence in remnant thyroid.
Jeon <i>et al.</i> [70]	cT1aN0M0 255 patients	Median, 94.8 months	Lobectomy 127 patients, total 128 patients	Local DFS rate	No significant difference in DFS rate ($p = 0.244$). Same findings after modulating confounding factors.

CIH: Cancer Institute Hospital; PTMC: papillary thyroid microcarcinoma; DFS: disease-free survival; CSS: cause-specific survival.

metastasis and those ≥ 50 years with significant extrathyroid extension (preoperative RLN paralysis, or invasion to the tracheal or esophageal mucosa), or lymph node metastasis ≥ 3 cm. All the other patients were classified into low mortality risk group [66]. Thus, these include intermediate- and high-risk patients in part in this guideline. As for 498 low mortality risk patients according to the classification system, 10-year disease-free survival (DFS) rates in the total thyroidectomy group (47 patients) and non-total thyroidectomy group (451 patients) were 95.7% and 89.2%, respectively, and cause-specific survival (CSS) rates in these groups were 99.2% and 100%, respectively, showing no significant differences [66]. Further, Ebina *et al.* showed that, in a prospective cohort study of 967 low-risk PTC patients based on the CIH classification, 10-year cause-specific and disease-free survival rates in the non-total thyroidectomy group (791 patients) were 99% and 87%, with no significant differences from the rates of 99% and 91% in the total thyroidectomy group [67]. Incidences of permanent hypoparathyroidism were reported as 9%, 5%, and 3% for patients who underwent total, near-total, and subtotal thyroidectomies, respectively. Permanent recurrent laryngeal nerve paralysis occurred in 3%, 3%, 2%, and 2% of patients who underwent total, near-total, and subtotal thyroidectomies and lobectomy, respectively; no significant difference was detected between total and

non-total thyroidectomy groups.

A report from Korea compared total and non-total thyroidectomies for patients with very low-risk PTC (T1aN0M0). Kim *et al.* analyzed a hemithyroidectomy group of 3,289 patients and a total thyroidectomy group of 5,387 patients and reported that total thyroidectomy reduced the risk of local recurrence after surgery, but did not influence the overall risk of recurrence except to the remnant thyroid [68]. Kwon *et al.* investigated the prognosis of lobectomy and total thyroidectomy groups (688 patients each) after 1:1 matching and found that the total thyroidectomy group achieved better recurrence-free survival [69]. However, after excluding recurrence to the remnant thyroid, the significant difference in recurrence rates between groups disappeared [69]. Regarding surgical complications, although the rate of recurrent laryngeal nerve injury did not differ between the two groups, permanent hypoparathyroidism occurred in 1.7% of the total thyroidectomy group. A comparative study by Jeon *et al.* of 127 patients in a lobectomy group and 128 patients in a total thyroidectomy group found no significant difference between groups [70].

A meta-analysis of 13 manuscripts by Zhang *et al.* concluded that, in PTC ≤ 2 cm, total thyroidectomy did not contribute to improvement of overall survival. Non-total thyroidectomy groups showed a higher recurrence rate, frequently as recurrence to the remnant thyroid [71].

Several manuscripts have been published regarding the relationship between the extent of thyroidectomy and health-related QOL, but the results were mixed (Table 7). Bongers *et al.* reported that although health-related QOL did not differ according to the extent of thyroidectomy, patients who received lobectomy showed stronger anxiety regarding recurrence [72]. However, one study detected no significant difference between the two groups [73], and another reported that patients with total thyroidectomy had more frequent complaints regarding health-related QOL [74]. Further, although a total thyroidectomy group showed more anxiety at 1–3 months after surgery, no difference between groups was detected beyond 6 months [75]. Either way, the influence of lobectomy on health-related QOL does not appear ruinous, and lobectomy is therefore recommended for low-risk PTC if the pathological lesion is limited to a single lobe.

Maki *et al.* reported that patients with low postoperative free-triiodothyronine (FT3) experienced more severe fatigue [76]. FT3 is known to be low if TSH is not suppressed after total thyroidectomy [77], so careful attention in postoperative management is required.

CQ 2-3.

Is prophylactic dissection of the lateral compartment recommended for cN0 or cN1a PTC?

Recommendation statement

For cN0 or cN1a PTC with no factors suggestive of poor prognosis such as large tumor size or extrathyroidal extension, prophylactic lateral compartment dissection is not recommended.

Certainty of evidence: B

Strength of recommendation: Weak; **Consensus rate:** 89%

Outcomes considered

- Recurrence rate
- Surgical complications
- Health status from the patient's perspective

Evidence

- Although clinically diagnosed as cN0/cN1a, pathological metastasis in the lateral compartment was detected at high prevalence when dissection was performed. This prevalence was 40.5% even for papillary thyroid microcarcinoma measuring ≤ 1 cm, and reached 86.5% in cases >4.0 cm.
- In retrospective studies of cases with no high-risk

Table 7 Comparison between extent of thyroidectomy and QOL

Authors	Patients and methods	Surgical designs	Outcomes
Bongers <i>et al.</i> [72]	Evaluation of QOL in 270 ATA low-risk DTC patients by EORTC QLQ-C30 version 3.0 and EORTC QLQ-TJY34 version 2.0. ASC	Total/near-total 211 patients Non-total 59 patients	Total scores in QLQ-C30 did not differ by surgical design ($p = 0.450$). Patients with lobectomy were more worried about recurrence ($p = 0.021$).
Yang <i>et al.</i> [73]	QOL of DTC patients evaluated by EORTC QLQ-C30 THYCA QOL.	133 patients after propensity score matching were evaluated; 54 underwent total thyroidectomy.	Regardless of analysis approach, QOL did not differ significantly between total and lobectomy groups.
Nickel <i>et al.</i> [74]	QOL of patients with total thyroidectomy and lobectomy was evaluated by originally developed HRQOL.	Of 1,005 DTC patients, 889 had PTC (88.6%) and lobectomy was performed for 214 patients (21.3%).	Total thyroidectomy group had more complaints regarding HRQOL. Adopting lobectomy for cases not significantly advanced may reduce patient anxiety and adverse events
Chen <i>et al.</i> [75]	HRQOL of low-intermediate risk DTC patients evaluated using EORTC QLO-C30 and THYCA QOL.	Between 563 patients with lobectomy and 497 with total thyroidectomy, QOL was compared at pre-operation, postoperative 1, 3, 6, and 12 months.	Although complaints based on HRQOL were more frequent in the total group than in the lobectomy group at 1 and 3 months after surgery, no difference was seen after 6 months later.
Maki <i>et al.</i> [76]	QOL of 292 thyroid carcinoma survivors analyzed in a cross-sectional study. CFS, SF36 version 2.0 were used.	Total thyroidectomy in 135 patients, others in 157 patients.	Patients with low FT3 experienced more tiredness.

DTC: differentiated thyroid carcinoma; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life core Questionnaire; ASC: Assessment of Survivor Concerns; THYCA-QOL: thyroid cancer-specific health-related quality of life questionnaire; CFS: Cancer Fatigue Scale; HRQOL: health-related quality of life.

features such as large tumor or extrathyroidal extension, prophylactic dissection of the lateral compartment was not reported to improve patient prognosis.

- Although the incidence is not high, various complications may occur with prophylactic dissection of the lateral compartment.
- Among series including cases with lateral compartment dissection, one study on patient perspectives showed that postoperative symptoms such as neck discomfort gradually reduced over time with neck stretching from immediately after surgery.

Summary and discussion of the literature

PTC metastasizes not only to the central compartment, but also to the lateral compartment at high incidence. According to a meta-analysis by Mulla *et al.*, among 2,048 cases who underwent prophylactic dissection of the lateral compartment, lateral node metastases were pathologically detected in 1,177 patients (57.5%), and these were diagnosed as pN1b [56]. In a study included in that meta-analysis, the rate of metastasis to the lateral compartment was related to tumor size, at 40.5% for PTC ≤ 1 cm, and reaching 86.5% for PTC > 4 cm [78]. However, pathological lymph node metastasis was present, but did not always manifest as clinical recurrence.

Ito *et al.* analyzed 1,231 cases with cN0 or cN1a PTC who underwent thyroidectomy, central compartment dissection and prophylactic lateral compartment dissection [78]. They reported that 10-year lymph node recurrence-free survival rates of patients with 0, 1, 2, and 3 of four factors (male sex, age ≥ 55 years, tumor size > 3 cm, and extrathyroidal extension corresponding to T4a) were 98.4%, 95.6%, 88.5%, and 64.7%, respectively (average follow-up, 10.9 years) [78]. Ducoudray *et al.* performed total thyroidectomy and central and bilateral lateral compartment dissection for 603 cases of cN0 PTC. Twenty-three cases (4%) showed recurrence during follow-up (average, 4.3 years). The recurrence rate was significantly higher in pN1b cases than in pN0 or pN1a cases [79]. Sugitani *et al.* implemented a prospective study in which only central compartment dissection was performed for cN0/N1a cases, and therapeutic lateral compartment dissection was added for cN1b cases [80]. The 10-year lymph node recurrence-free survival rate in the former group was good, at 91%, and cases that showed recurrence to lateral nodes obtained local cure with reoperation. None of these patients died of thyroid carcinoma during postoperative follow-up (average, 8.1 years). For cN0/N1a cases, distant metastasis at diagnosis (risk ratio, 46) and primary lesion > 4 cm (risk ratio, 3.6) were risk factors for lymph node recurrence.

No prospective studies have directly compared prognoses between patients with and without prophylactic dissection of the lateral compartment and all studies were

retrospective. The consistent conclusion was that prophylactic lateral compartment dissection did not improve the risk of PTC recurrence in cases without high-risk features such as large tumor size or extrathyroidal extension corresponding to T4a [81, 82]. Further, Ito *et al.* reported that although treatment plans in their institutions changed in 2006, resulting in significantly decreased application of prophylactic lateral compartment dissection, lymph node recurrence-free survival rates still improved [82]. They considered that possible reasons for these findings were: 1) the incidence of cases with large tumor size or extrathyroidal extension was reduced as compared with the past; and 2) significant improvements in the accuracy of imaging studies such as ultrasound over time.

Although the incidences are low, various complications might occur with prophylactic dissection of the lateral compartment. Ito *et al.* reported chyle leakage requiring reoperation, lymphorrhea requiring drainage, phrenic nerve injury, facial nerve paralysis, accessory nerve paralysis, Horner syndrome, and pneumothorax occurring in 0.6%, 1.0%, 0.2%, 0.3%, 0.2%, 0.2%, and 0.08% of patients, respectively [78]. Wound extension is also inevitable with dissection of the lateral compartment, exacerbating neck pain and discomfort. Takamura *et al.* reported that, for these complaints, neck-stretching exercises from the day after surgery appear useful [83].

Taken together, for cN0/N1a PTCs with no factors indicative of poor prognosis, prophylactic dissection of the lateral compartment is not recommended.

Note 2-2. Are aggressive therapies including total thyroidectomy recommended for intermediate-risk PTC for old patients?

Intermediate-risk PTC is defined as PTC showing no extension to adjacent organs from the primary tumor or metastatic lymph nodes, a tumor diameter of 2.1–4 cm, or clinical node metastasis ≤ 3 cm in diameter (Table 2).

In 2020, Ito *et al.* conducted a subset analysis of 1,230 high-risk and 1,798 intermediate-risk PTCs by dividing patients into groups ≥ 55 and < 55 years old [30]. The prognosis of intermediate-risk PTC was poorer in old patients than in young patients, but 10- and 20-year CSS rates were still high, at 99.1% and 96.9%, respectively. Total thyroidectomy was performed for 976 patients (54.3%), but only 22 patients (1.2%) were administered RAI ≥ 30 mCi. During postoperative follow-up (median, 176 months; range, 3–357 months), only 18 patients (1.0%) died of thyroid carcinoma.

Matsuzaki *et al.* analyzed 1,088 PTCs who underwent lobectomy as initial surgery, and reported 10- and 20-year distant recurrence rates of 1.4% and 3.7%, and carcinoma death rates of 0.6% and 2.2%, respectively [84].

Only 22 patients (2.0%) died of thyroid carcinoma and all had at least one of the following four factors: 1) age ≥ 45 years; 2) tumor diameter > 4 cm; 3) N1; and 4) extrathyroidal extension corresponding to T4a.

Ebina *et al.* analyzed 967 PTCs measuring > 1 cm classified as low risk according to the CIH classification, and reported that disease recurrence-free survival rates and CSS rates did not differ significantly between 170 patients who underwent total thyroidectomy and 791 patients who received non-total thyroidectomy [67].

McKinney *et al.* extracted cT2N0M0 cases from the National Cancer Database, and analyzed overall survival (OS) rates [85]. In the subset > 55 years old, patients who received total thyroidectomy and RAI showed a better OS rate than those who underwent lobectomy. However, whether surgical design truly affects the prognosis of thyroid carcinoma itself remains unclear.

Taken all together, although the prognosis of PTC with intermediate-risk patients ≥ 55 years old is certainly poorer than that of young patients, 10- and 20-year cancer mortality rates are still excellent, at 0.9% and 2.6%, respectively. Aggressive therapies such as total thyroidectomy, extensive lymph node dissection, and RAI therapy therefore should not be uniformly recommended, and the surgical design and postoperative adjuvant therapy (*e.g.*, RAI administration, *etc.*) should be decided on a case-by-case basis by considering factors such as the status of primary and metastatic lesions, cytological findings, general status of the patient including cognitive function, and life expectancy.

Column 2-2. Significance of total thyroidectomy for PTC

Actually, the kind of PTC indicated for total thyroidectomy remains a rather difficult issue. To date, few retrospective studies have been published investigating whether and how total thyroidectomy improves the prognosis of PTC patients. Ito *et al.* analyzed 2,638 PTCs with T1N0M0 and reported that the prognosis of carcinoma recurrence in cases with non-total thyroidectomy was poorer than that in cases with total thyroidectomy [65]. However, prognoses of the two groups became similar after excluding recurrence to the remnant thyroid [65]. Ebina *et al.* reported that in the group at low risk of carcinoma death according to the CIH classification (see CQ2-2), whether total or non-total thyroidectomy was performed was unrelated to disease-free and cause-specific survivals. Further, age ≥ 60 years, tumor size ≥ 3 cm and lymph node metastasis ≥ 2 cm were independent risk factors for distant recurrence on multivariate analysis of the low-risk group. Give these findings, Ebina *et al.* considered that, in low-risk cases lacking risk factors for distant recurrence, total thyroidectomy is

not mandatory [67]. Sugitani *et al.* reported that, in the subset of high-risk cases according to “Clinical Practice Guidelines on the Management of Thyroid Tumors 2018”, no significant differences in prognosis regarding recurrence and carcinoma death were detected between total and non-total thyroidectomy groups even after matching for background factors [86]. Further, on multivariate analysis, extent of thyroidectomy was not recognized as an independent prognostic factor [86]. Ito *et al.* analyzed 1,230 high-risk cases based on the same guidelines, and reported that although prognostic factors for CSS differed significantly between patients ≥ 55 years old and those < 55 years old, extent of thyroidectomy was not an independent prognostic factors in either group [30].

Studies from other countries have compared prognosis for PTC or differentiated thyroid carcinoma (DTC) between cases that underwent total or non-total thyroidectomy. However, studies extracting cases from large-scale databases [87-90] and single-institution studies [91-93] concluded that cases with total thyroidectomy did not show better prognosis than cases with non-total thyroidectomy.

The availability of serum thyroglobulin (Tg) test as a useful postoperative tumor marker is a key benefit of total thyroidectomy. When the Tg value increases over time, systemic examinations such as RAI administration and positron emission tomography-computed tomography are performed, and RAI therapy can be implemented after early detection of metastatic/recurrent lesions. Total thyroidectomy can thus prove highly convenient for postoperative management as opposed to directly improving patient prognosis. On the other hand, as a demerit, total thyroidectomy increases the risk of significant surgical complications such as bilateral vocal cord paralysis or permanent hypoparathyroidism, particularly for high-risk cases. In the future, the development of therapies targeting driver gene mutations and genetic examinations for use in the early phase of treatment to predict response to RAI therapy might further change the significance of total thyroidectomy.

Column 2-3. Not performing prophylactic central compartment dissection

The “Clinical Practice Guidelines for Thyroid Tumors 2018” contain the clinical question “Is prophylactic lymph node dissection recommended in the surgery of PTC?” with the answer that “Prophylactic central node dissection is recommended”. As reasons for this recommendation: 1) a meta-analysis demonstrated that prophylactic central compartment dissection reduces the recurrence rate; 2) since the central compartment is located in the same surgical field as thyroidectomy,

dissection of this compartment is not time-consuming; and 3) the surgical complications of reoperation for recurrence to the central compartment might be increased if adhesions from previous surgery are present. However, a considerable number of meta-analyses have been published to date, and the conclusions have been inconsistent regarding whether prophylactic dissection of the central compartment influences patient prognoses and the frequency of adverse events [94–101]. This is likely because many of the studies covered by meta-analyses were retrospective studies that included various biases. Whether prophylactic dissection of the central compartment is useful for cases lacking high-risk features such as clinical lateral node metastasis, large tumor size, and extension to adjacent organs remains an open question. According to Ito *et al.*, 5- and 10-year central node recurrence-free survival rates were excellent for 4,301 cases of cN0M0 PTC in which prophylactic dissection of the central compartment was routinely performed along with thyroidectomy, at 99.1% and 98.2%, respectively [102]. However, this was a result from a

single-arm study for patients who underwent node dissection, and cannot be used as a foundation for recommending prophylactic dissection of the central compartment.

In 2012, Carling *et al.* calculated that 5,840 patients would have to be enrolled to achieve at least 80% statistical power in a prospective randomized study of the significance of prophylactic central compartment dissection for cN0 PTC. Thus, they concluded that a prospective randomized controlled trial of this subject is not readily feasible [103]. Five prospective randomized studies [104–108] (Table 8) and two meta-analyses of those studies [109, 110] have since been published. Although the numbers of enrolled patients were small, at 60–257 cases, prognosis did not differ between dissection and non-dissection groups. Conclusions have been inconsistent regarding differences in adverse events between groups [105–108], but all the studies agreed that prophylactic dissection of the central compartment offered no clear oncological benefit.

As shown in tentative calculations by Carling *et al.*,

Table 8 Prospective randomized studies of surgeries with and without prophylactic central compartment dissection

Authors	Subjects	Follow-up	Surgical designs	Results
Kim <i>et al.</i> [104]	Low-risk PTMC 164 patients	Average, 73.4 months	All hemithyroidectomy, dissection (+) 82 patients; dissection (–) 82 patients	Shorter surgery time for dissection (–) ($p < 0.0001$). Postoperative Tg was higher with dissection (–) ($p = 0.005–0.037$). No difference in recurrence rate was seen between the two groups.
Lee <i>et al.</i> [105]	T1-T2N0 PTC 257 patients	Dissection (+) 55.2 months; (–) 49.2 months (median)	All total thyroidectomy Dissection (+) 153 patients; (–) 104 patients	Hypothyroidism more frequently ($p = 0.043$) occurred in the dissection (+) group. For other adverse events and recurrence rate, no differences were detected.
Viola <i>et al.</i> [106]	cN0 PTC 181 patients	Average, 59.4 months	All total thyroidectomy Dissection (+) 93 patients, (–) 88 patients	No difference between backgrounds, <i>etc.</i> Tg value after RAI ablation lower in the dissection (+) group ($p = 0.0017$). Hypothyroidism more frequent in the dissection (+) group ($p = 0.023$). Clinical outcomes did not differ between these two groups.
Sippel <i>et al.</i> [107]	cN0 PTC 60 patients	Not described?	All total thyroidectomy Dissection (+) 31 patients, (–) 30 patients	Excellent response to therapy was achieved in 81% of the dissection (+) group and 80% of dissection (–) group. Rates of achieving Tg <0.2 ng/mL and stimulated-Tg <1.0 ng/mL at 6 weeks and 1 year later were almost the same. The incidence of surgical adverse events did not differ.
Ahn <i>et al.</i> [108]	cN0 PTC 101 patients Age, 20–70 years	Average, 46.6 months	All total thyroidectomy Dissection (+) 51 patients, (–) 50 patients	No patients in the two groups showed recurrence on imaging. Incidences of surgical complications and achievement of RAI ablation were almost the same.

answering this question based on a high level of evidence is not easy, and remains a subject for future clarification. However, in view of the lack of difference in recurrence rates in prospective randomized studies (despite the small number of patients) and the possibility of an increased incidence of adverse events from dissection (or no decrease, at least), uniformly recommending prophylactic dissection of the central compartment is considered inappropriate. Whether adverse events such as vocal cord paralysis and hypoparathyroidism occur after dissection shows a significant dependence on the skills of the surgeons involved. Prophylactic central compartment dissection for cN0 PTC is thus not mandatory and should be individually considered based on the background of the patient (age, physical status, *etc.*) and the skill of the surgeons.

Note 2-3. Serum thyroglobulin (Tg) monitoring for postoperative PTC

Tg is regarded as an important tumor marker for differentiated thyroid carcinomas negative for thyroglobulin antibody (TgAb). In cases of total thyroidectomy, Tg should theoretically fall below the limits of detection if curative surgery is achieved. However, depending on the case, minute areas of normal thyroid tissue may remain at the circumference of the ostia of the recurrent laryngeal nerve. In such situations, Tg may be measurable. Tg definitely becomes high when thyroid carcinoma remains undissected or metastasizes to local regions or distant organs. In the guidelines developed by the American Thyroid Association (ATA), cases with Tg ≥ 1 ng/mL (or ≥ 10 ng/mL under stimulation by recombinant human thyroid-stimulating hormone [rhTSH]) are judged as showing “biochemical incomplete response”, and 20% will show apparent recurrence on imaging studies (structural disease) [111].

Studies from countries where RAI therapy can be actively performed have shown that Tg levels both before and after RAI administration are related to prognosis [112] and relationships between Tg levels under rhTSH stimulation and prognosis have been reported [113–116]. However, these insights are not considered particularly useful for clinical practice in Japan, where RAI therapy has not been widely adopted. Rather, measuring postoperative Tg constantly and evaluating the change in Tg levels over time is important (see Note 3-4). The prognosis of cases with a Tg-doubling time (DT) < 1 year is very dire [117]. For cases showing constant elevation of Tg with time after surgery, RAI administration and imaging studies should be performed under suspicion of carcinoma recurrence.

In TgAb-positive cases, the value of Tg as a tumor marker is decreased. For such cases, both Tg and TgAb

should be measured simultaneously and monitored. According to Tsushima *et al.*, lymph node and distant recurrence-free survival rates were significantly better in cases showing a decrease in TgAb level $\geq 50\%$ from pre-operative levels after total thyroidectomy, as compared with other cases [118]. RAI administration and imaging studies such as PET should thus be performed under suspicion of recurrence in cases not showing definitive decreases in TgAb or re-elevation of TgAb after an initial decrease.

Various studies have investigated changes in Tg levels after lobectomy. Chou *et al.* included four studies in a systematic review, but concluded that whether carcinoma recurrence is present could not be accurately determined because the positive predictive value and sensitivity were low, whereas the negative predictive value and specificity were high, and because Tg values did not differ significantly between cases with and without recurrence [119]. However, Xu *et al.* showed that cases with initial Tg values 6–12 months after lobectomy ≥ 5.3 ng/mL or last Tg levels ≥ 11.0 ng/mL were more likely to show recurrence [120]. Considerably large amounts of thyroid remain undissected after lobectomy, so the value of Tg as a tumor marker is rather lower compared with cases after total thyroidectomy. However, recurrence should be suspected if an elevation of Tg level over time is detected. Therefore, even for cases after lobectomy, regular Tg and TgAb measurements are recommended.

Note 2-4. Evaluation by dynamic markers for PTC recurrence

In PTC, several important prognostic factors that should be evaluated pre- and intraoperatively have been identified, including age, tumor size, N factor, M factor, and tumor extension. The present guideline also establishes a risk classification system by combining these factors. However, postoperative status should be evaluated by factors subject to moment-to-moment changes (dynamic markers).

Several studies have reported on dynamic markers for recurrent PTC, and three representative examples are listed here. These can be applied for not only PTC, but also follicular thyroid carcinoma (FTC).

1) Tg doubling time (Tg-DT) and Tg doubling rate (Tg-DR) in TgAb-negative cases

In 2011, Miyauchi *et al.* calculated the time required for Tg concentrations to double in TgAb-negative cases that underwent total thyroidectomy, establishing the concept of Tg-DT [117]. As a consequence, the 10-year CSS rate of cases with a Tg-DT < 1 year was found to be low, at only 50%, but that of patients with a Tg-DT of 1–3 years was high, at 95%. Further, multivariate analysis together with various other static factors identified a

Tg-DT <1 year as an independent predictor of death from carcinoma. However, since Tg can either increase or decrease, the continuity of values disappears if cases showing a Tg increase and those showing a Tg decrease are analyzed together. Thus, subject to the approach applied by Barbet *et al.* [121], evaluation using the inverse of Tg-DT can evaluate cases with Tg increases and decreases together in a single group. Miyauchi *et al.* termed this the Tg-DR, using units of “per year”. Among 321 DTCs with distant metastasis in 2021 (253 PTCs, 690 FTCs, and 8 poorly differentiated carcinomas), Ito *et al.* demonstrated that 256 were negative for TgAb. For these, the CSS of cases was significantly poorer with a Tg-DR >1/year than with a Tg-DR ≤1/year. Further, Tg-DR >1/year provided an independent predictor of carcinoma death on multivariate analysis [122].

Although the methodology for calculating Tg-DT/Tg-DR is rather complicated, calculation software can be downloaded from the homepage of Kuma Hospital, making the calculation easy simply by assigning values (<https://www.kuma-h.or.jp/kumapedia/kuma-medical/detail/id=59>).

2) Tumor volume doubling time (TV-DT) and tumor volume doubling rate (TV-DR)

This is a concept established under the hypothesis that the speed of growth of metastatic/recurrent tumors affects patient prognosis. In particular, lung metastases can be measured in at least two dimensions with comparative ease on CT, and TV-DT is easily calculated by assigning the requisite values in the above calculation software; evaluation of TV-DR is considered appropriate for the same reasons given above. However, accurate measurement may be difficult for some metastases, such as bone metastasis, and evaluation may thus prove impossible. In a series of 292 DTCs for which TV-DR could be calculated, TV-DR >1/year represented a predictor of poor CSS both on uni- and multivariate analyses [122].

3) Neutrophil/lymphocyte ratio (NLR)

NLR has been reported as a strong prognostic factor for carcinomas in various organs. Although the mechanisms involved remain unclear, systemic inflammation may be related to carcinoma progression. Some studies have been published regarding the relationship between NLR and the prognosis of thyroid carcinoma, but no findings useful for daily clinical practice were obtained. However, focusing on DTC showing distant metastasis/recurrence, cases with NLR >3 at the detection of distant metastasis/recurrence showed a significantly more dire prognosis than those with NLR ≤3 [122], and thus may merit consideration when molecularly targeted therapy is initiated [123, 124].

Based on these findings, NLR offers a static marker,

but 5- and 10-year survival rates from the time of NLR reaching >3 under regular follow-up were very low, at 50.4% and 23.9%, respectively [122]. NLR is likely to be associated with disease progression, and may provide a useful criterion for gauging the efficacy of molecularly targeted agents.

Note 2-5. Controlling TSH in PTC patients after surgery

To date, some reports have been published regarding the relationship between postoperative TSH values in PTC (or DTC) and patient prognoses. At this point, only one randomized comparative study was from Japan, with Sugitani *et al.* assigning 433 PTC patients to a TSH suppression group (<0.01 μ IU/mL) or control group (within normal limit), and conducted follow-up for a mean of 6.9 years [125]. Accordingly, no significant differences were found in 5-year DFS and CSS between these two groups. In that report, only 50 cases (11%) were classified as high risk (AMES classification) and only 66 cases (11%) underwent total thyroidectomy.

Hovens *et al.* performed a prospective study (median follow-up, 8.9 years) for 366 DTC cases that received RAI ≥2,800 MBq, and reported that cases with median TSH ≥2 μ IU/mL showed poorer DFS and CSS [126]. A study of 4,941 DTCs (85% underwent total/near total thyroidectomy and 71% received RAI administration) by Carhill *et al.* reported that cases with a TSH concentration 3.0–4.0 mIU/L (normal or elevated) showed poorer prognosis than others at every stage. However, no significant difference in prognosis was detected between patients with TSH concentrations 2.0–2.9 mIU/L (sub-normal) and those with 1.0–1.9 mIU/L (undetectable) [127]. Conversely, Wang *et al.* reported that in 771 cases of DTC showing low or intermediate risk according to the ATA guidelines, the prognosis of patients with TSH suppressed to ≤0.4 μ IU/mL did not differ from that of other patients [128]. In 2019, a retrospective study for 1,528 patients with PTC who underwent lobectomy followed-up for an average of 5.6 years found that TSH value did not affect carcinoma recurrence [129]. Another retrospective study in 2021 showed that TSH level was a predictor of PTC recurrence along with *BRAF* mutations and lymph node metastasis, but the surgical designs were not uniform [130].

Adverse events of TSH suppression include osteoporosis and cardiovascular diseases. Although great variability has been seen among the results of previous reports [131], multiple recent investigations have supported these relationships [125, 128, 132–134]. In contrast, one report indicated that although FT3 levels fall within normal limits under mild TSH suppression, significant decreases are seen with normal TSH levels,

resulting in the same situation as under hypothyroidism [77].

Taken together, appropriate postoperative TSH levels are summarized as follows:

- 1) TSH suppression after lobectomy lacks clinical significance, and should not be performed;
- 2) In low-risk cases that undergo total thyroidectomy, TSH suppression does not contribute to improving prognosis. However, setting TSH at low normal or very mildly suppressed seems meaningful to preserve FT3 level within normal range;
- 3) After total thyroidectomy for high-risk cases, TSH suppression is recommended to prevent metastasis/recurrence. However, suppression of TSH below the limit of detection should not be performed because patient prognosis is not improved and adverse events are induced; and
- 4) Whether and how to apply TSH suppression for intermediate-risk patients after total thyroidectomy should be decided individually according to intra-operative findings, pathological findings, age, and the general condition of the patient.

Chapter 3. Follicular tumor

Clinical algorithm 3-1. Initial treatment for follicular tumor (Fig. 5)

CQ 3-1.

For which follicular tumors is surgery recommended?

Recommendation statement

Surgery is recommended for follicular tumors with a cytological diagnosis of Category IV (follicular neoplasm) according to the Bethesda system, if any of the following conditions are present:

- (1) High-grade cytological malignancy;
- (2) Suspected malignancy on ultrasound (US);
- (3) Large tumor diameter (>3–4 cm); or
- (4) Rapid tumor growth.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 67%

Outcomes considered

- Probability of malignancy diagnosis
- Prognosis
- Surgical complications

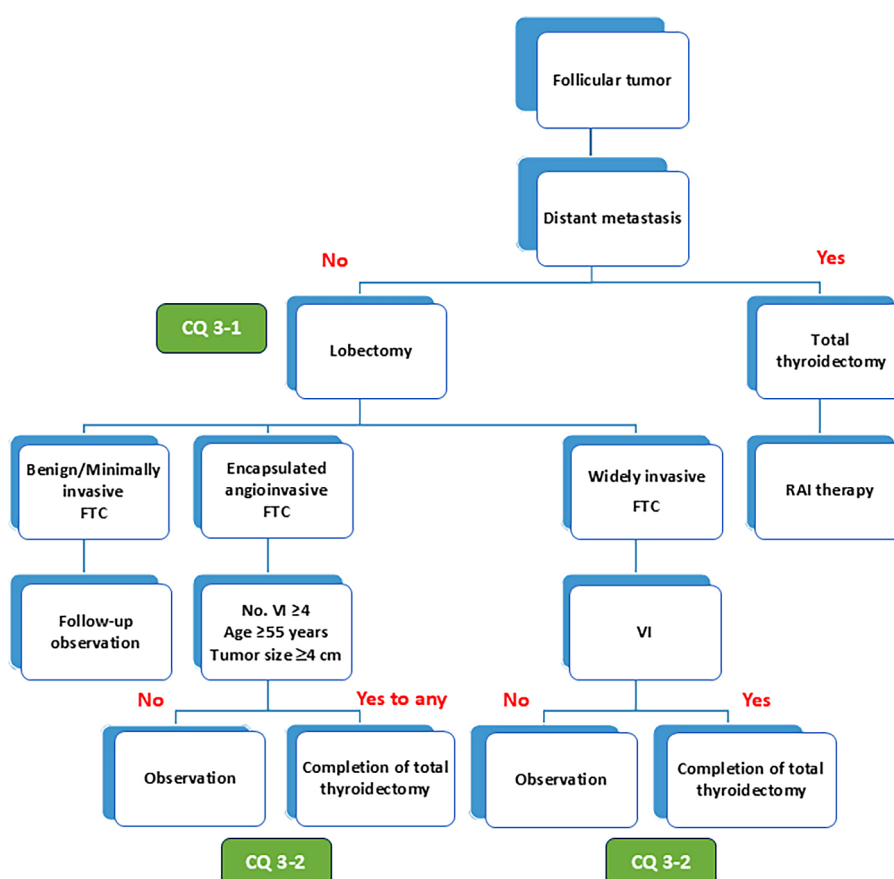


Fig. 5 Clinical algorithm 3-1. Initial treatment for follicular tumor

FTC: follicular thyroid carcinoma; RAI: radioactive iodine; VI: vascular invasion.

- Health conditions from the patient's perspective

Evidence

- Although US and FNAC show some utility as diagnostic modalities, no reliable preoperative method has been developed to diagnose FTC.
- Some reports have suggested that cytological findings, US findings, tumor size, and speed of growth contribute to the likelihood of malignancy, while others have denied this.
- No reports have clarified health status from the patient's perspective.

Summary and discussion of the literature

FNAC and US are useful in distinguishing between benign and malignant thyroid nodules. However, no tests are available that can diagnose FTC preoperatively with a high degree of accuracy, and the final diagnosis is based on histological findings. As a result, no prospective studies on the preoperative diagnosis of FTC are available, and all studies have been retrospective.

Several reports have examined the diagnosis of FTC by US and FNAC. In a study by Sugino *et al.* that investigated the postoperative histological diagnosis and preoperative laboratory findings in patients who underwent surgery without obvious preoperative malignant findings, approximately 35% of cases diagnosed as “follicular tumor” or “indeterminate” by US and FNAC were diagnosed as FTC after surgery, and approximately 5% of cases diagnosed as benign (hyperplasia) by both the above tests were found to have FTC [135]. Kihara *et al.* also reported that among 541 patients with nodules diagnosed as benign by cytology, 16 patients (3.0%) were diagnosed with malignancy postoperatively, 12 of whom had FTC. The same study found no significant differences in age, sex, mass diameter, Tg level, or TV-DT between benign and malignant cases, with significant differences only in ultrasound findings [136]. Since most patients are followed-up without surgery if the diagnosis is non-malignant, only a few undergo surgery and substantial bias is present in the above reports, various limitations to current preoperative testing are evident. In a report from South Korea that limited analysis to cases cytologically diagnosed as “follicular tumor”, 100 cases underwent operation after more than 1 year of follow-up and the relationship between postoperative pathology and TV-DT was examined [137]. No significant difference in TV-DT was seen between benign and malignant tumors according to final histological diagnosis. Comparing the frequency of cases with a >50% increase in tumor volume over time, no difference was apparent between benign and malignant tumors, nor was any significant difference in tumor size or various ultrasound diagnostic classifications seen between groups.

In a report by Hirokawa *et al.* [138], 356 cases diag-

nosed as follicular tumor by cytological diagnosis were classified as “favors malignant”, “borderline”, or “favors benign”, of which 41.2%, 8.2%, and 7.7% were malignant according to histological diagnosis, respectively. Further, the malignancy rate was 14.6% in patients with one or more of the four findings suggestive of malignancy (cytological findings favoring malignancy, tumor diameter >3 cm, TV-DR >1.0/year, and US findings of suspected malignancy), compared with 1.4% in patients with none of these findings. The authors therefore concluded that follicular tumors without these findings are acceptable for follow-up. That report did not focus exclusively on FTC, but did suggest an appropriate direction for routine clinical practice as an approach to nodules thought to represent follicular tumor preoperatively.

In several countries, molecular diagnosis has been applied clinically to cases difficult to differentiate based on cytology. In a study of cases with molecular diagnosis (ThyroSeq® v2 or v3) of 405 nodules diagnosed as follicular tumor by cytology [139], 139 nodules showed genetic mutations suggestive of malignancy, and 215 nodules did not. Of the 218 nodules for which surgery was performed, 109 (50%) were malignant. In cases with positive molecular diagnosis, 70% were malignant, whereas the malignancy rate in negative cases was only 16% ($p < 0.0001$). However, only 15 nodules (6.9%) of operated cases were FTC (including oncocytic cell type). Although molecular diagnosis is useful to some extent in predicting malignant nodules, the evidence for sufficiently accurate preoperative diagnosis of FTC remains insufficient.

CQ 3-2.

Is completion total thyroidectomy recommended for FTC diagnosed after lobectomy?

Recommendation statement

- 1) Completion total thyroidectomy is not recommended for minimally invasive FTC.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 100% (re-vote)

- 2) Completion total thyroidectomy is recommended for encapsulated angioinvasive FTC either when the number of vascular invasions is ≥ 4 , age is ≥ 55 years, or primary tumor diameter is > 4 cm.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 78%

- 3) Completion total thyroidectomy is recommended for widely invasive FTC with vascular invasion.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 67%

Outcomes considered

- Prognosis
- Surgical complications
- Health conditions from the patient's perspective

Evidence

- Distant metastasis (recurrence) is a powerful prognostic factor in FTC.
- Minimally invasive FTC shows a very excellent prognosis, and routine completion total thyroidectomy is not recommended.
- In encapsulated angioinvasive FTC, the number of vascular invasions, age, and tumor diameter represent risk factors for distant recurrence. When these factors are present, completion total thyroidectomy is recommended to prepare postoperative RAI.
- Widely invasive FTC with vascular invasion is at high risk of distant recurrence and completion total thyroidectomy is recommended.
- Evidence remains lacking for improved prognosis from completion total thyroidectomy.
- No significant difference in the frequency of complications is seen between cases of initial total thyroidectomy and total thyroidectomy completed after initial lobectomy.

Summary and discussion of the literature

A major prognostic factor of FTC is distant metastasis [140–142]. In patients with risk factors for distant metastasis, completion total thyroidectomy is recommended to detect recurrence earlier and to allow treatment by RAI. Prognostic factors for FTC are better understood when discussed by histological subtype. Formerly, minimally invasive type referred to cases showing minimal capsular invasion with or without vascular invasion, but according to the 4th edition of the WHO classification, minimally invasive type refers to cases with minimal capsular invasion without vascular invasion, while those with vascular invasion are classified under a separate category, encapsulated vascular invasive type. Therefore, in previous reports, the prognosis of these two types was examined collectively, and age, tumor diameter, and the number of vascular invasions were cited as risk factors for recurrence [141, 143–145]. In a 2021 report by Yamazaki *et al.*, the 10-year disease-specific survival rate and 10-year recurrence-free survival (RFS) rate in 111 cases of M0 minimally invasive type (capsular invasion only) were excellent, at 100% and 98% or more, respectively [146]. In a study of 285 cases of M0 minimally invasive FTC (under the former classification) by Ito *et al.* in 2013, age (≥ 45 years), tumor diameter (> 4 cm), and number of vascular invasions (≥ 4) were reported as factors significantly related to recurrence [141]. Few studies have examined the prognosis of encapsulated vascular invasive FTC alone, and evidence remains insufficient. The

number of vascular invasions has been reported as a risk factor for recurrence, with a cut-off of 4, but this has not been studied in detail. In a 2022 study of prognosis in 251 cases of M0 encapsulated vascular invasion type, Yamazaki *et al.* reported that the number of vascular invasions was significantly associated with recurrence, with a cut-off value of 2. Age was also a significant factor, with a significantly poor 10-year RFS rate of 66% reported for patients ≥ 55 years old and with 2 or more vascular invasions [147]. Further evidence is needed to determine the optimal cut-off value for the number of vascular invasions.

Widely invasive FTC shows a high incidence of distant recurrence and poor prognosis. For this reason, after histological diagnosis, completion total thyroidectomy is uniformly recommended. However, recent reports from Japan have shown that the absence or presence (and number) of vascular invasions is also related to distant recurrence in the widely invasive type. Ito *et al.* reported that out of 523 patients with FTC, widely invasive type was not a factor significantly associated with distant recurrence, but the degree of vascular invasion showed a strong association. The prognosis of patients with widely invasive carcinoma without vascular invasion (20-year distant recurrence-free rate, 97%) was significantly better than that of patients with extensive invasive carcinoma with vascular invasion (69%) or encapsulated vascular invasion (71–86%) [148]. Further, Yamazaki *et al.* reported the number of vascular invasions as a significant prognostic factor in a study of 107 patients with widely invasive type, with both 10-year disease-specific survival rate and 10-year distant metastasis-free recurrence rate of 100% in patients with no vascular invasion [149]. On the other hand, a report from South Korea found that the presence or absence of vascular invasion did not affect the prognosis of widely invasive type [142]. Although completion total thyroidectomy may not need to be uniformly required even for widely invasive type, further accumulation of evidence is necessary.

Likewise, evidence for whether completion total thyroidectomy contributes to improved prognosis remains insufficient. In a study by Sugino *et al.* of 324 patients who underwent lobectomy as initial surgery and were histologically diagnosed with minimally invasive follicular thyroid carcinoma (former classification), 101 patients underwent completion total thyroidectomy, while the remaining 223 patients were followed-up with lobectomy alone. Although patients with completion total thyroidectomy were significantly older, no significant differences in tumor size or degree of vascular invasion were seen between the two groups, and no significant differences in distant metastasis-free survival rate or disease-specific survival rate were identified

[150]. In that study, patient age was an important factor in performing completion total thyroidectomy, but it may be worth noting that no differences were apparent in the prognosis of older patients with completion total thyroidectomy compared to younger patients without completion total thyroidectomy, who display better prognosis to begin with.

Several reports have compared postoperative complications from completion total thyroidectomy with those from initial total thyroidectomy. In a large study using the National Surgical Quality Improvement Program Database in the United States, no difference in surgical complication rates was seen between the two [151]. While one report found no differences in transient or permanent recurrent nerve palsy or hypoparathyroidism between groups [152], another found more damage to the external branches of the superior laryngeal nerve in cases of completion total thyroidectomy [153]. Clear evidence that postoperative complications are more common with completion total thyroidectomy remains lacking.

Column 3-1. Oncocytic cell carcinoma (oxyphilic FTC) in Japan

Oxyphilic FTC was formerly termed Hürthle cell carcinoma, as Hürthle cells were described by Karl Hürthle, but these cells were later revealed to actually be C cells [154]. In the fifth edition of the WHO histological classification, this pathology is termed oncocytic carcinoma of the thyroid and has become an independent disease entity rather than the former classification as a subtype of FTC [155]. Oxyphilic cell follicular tumors consist of more than 75% oxyphilic cells and are classified as adenoma or carcinoma based on the presence or absence of capsular or vascular invasion, as is the case with regular FTC. Oxyphilic cell tumor is considered a relatively rare malignancy overseas, accounting for only 3–7% of thyroid cancers [156]. Although the exact incidence in Japan is unknown, reports from two Japanese centers have shown that the proportion of this disease in total FTC appears about the same, at around 15% [157, 158]. Since FTC itself reportedly represents about 5% of all thyroid cancers, this pathology is assumed to be relatively rare, and even less common than in other countries.

Previously, oncocytic cell carcinoma was reported to show poorer prognosis than other differentiated thyroid carcinomas [159, 160], but studies from Japan have shown no difference in prognosis compared with conventional-type FTC [148, 157]. Sugino *et al.* compared the prognosis of 485 patients with conventional FTC and 73 patients with oncocytic cell carcinoma, with patients with the conventional type being younger ($p = 0.001$), showing a more extensive invasive type ($p = 0.03$), and having more distant metastases on initial pre-

sentation ($p = 0.03$). In a multivariate analysis of risk factors for disease-specific survival in all patients, age, primary tumor size, and distant metastasis at initial presentation were significant factors, while histological subtype was not. There were also no significant differences in prognosis between normal and oncocytic cell carcinoma by age, degree of invasion, or tumor type [157]. A recent report by Ito *et al.* on the prognosis of 523 patients with FTC, including oncocytic cell carcinoma [148], found that non-oncocytic FTC (conventional FTC) was a significant factor in distant recurrence, as were age and number of vascular invasions, suggesting a more favorable prognosis for oncocytic cell carcinoma. A multicenter report from South Korea that compared prognosis between 80 cases of oncocytic cell carcinoma and 483 cases of normal FTC showed no difference in recurrence rate over a median follow-up of 72 months [161].

A report summarizing the literature on the prognosis of oncocytic cell carcinoma from 1940 to 2002 noted that 20.7% of cases died of the disease after an average follow-up of 8.7 years [162]. In a meta-analysis of reports from 2000 to 2020 [156], the 10-year recurrence-free survival rate was 80% (95%CI 70–89%) and the 10-year cumulative OS rate was 76% (95%CI 70–82%). The prognosis of oncocytic cell carcinoma has gradually improved, but no change in prognosis has been reported for normal FTC [163]. One suggestion is that reductions to iodine intake deficiency in Europe and the United States may have contributed to this improvement.

Chapter 4. Medullary thyroid carcinoma (MTC)

Clinical algorithm 4-1. Initial treatment for MTC (Fig. 6)

Clinical algorithm 4-2. Postoperative surveillance for MTC (Fig. 7)

Note 4-1: Static prognostic factors for MTC

1) Clinical prognostic factors

Regarding the prognosis of MTC, Clark *et al.* reported OS rates of 97%, 88%, and 84% at 5, 10, and 20 years, respectively, indicating favorable prognosis [164]. Poor clinical prognostic factors include older age and tumor size, as well as multiple lymph node metastases, distant metastasis, and extrathyroidal invasion [165–169].

2) Pathological prognostic factors

In a report by Xu *et al.* involving 327 patients undergoing initial surgery at five institutions, high-grade MTC was defined by the presence of any of the following criteria: 1) mitotic index ≥ 5 per 2 mm²; 2) Ki-67 labeling index $\geq 5\%$; and 3) presence of tumor necrosis. Other

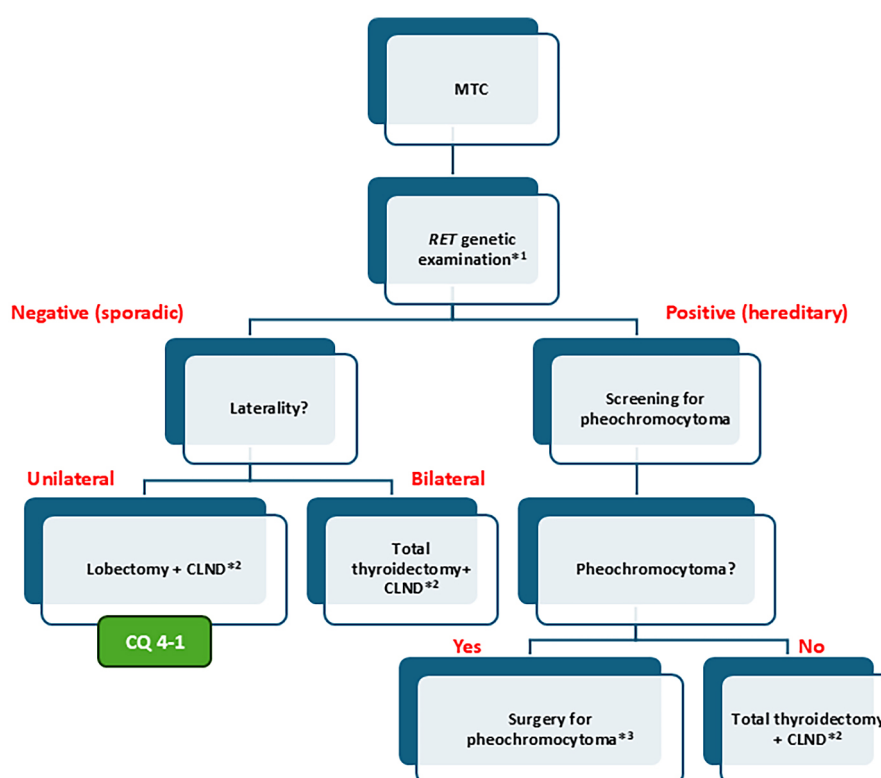


Fig. 6 Clinical algorithm 4-1. Initial treatment for medullary thyroid carcinoma (MTC)

*1 Confirmation of embryonic cell mutations.

*2 Central lymph node dissection is mandatory. Lateral lymph node dissection is principle to therapeutic dissection (see CQ 4-2).

*3 Basically, pheochromocytoma surgery is performed first, but depending on the degree of hormonal activity of the pheochromocytoma and the progression of MTC, surgery may be performed first if the environment is conducive to intraoperative pheochromocytoma crisis after thorough consultation with endocrinologists and anesthesiologists.

CLND: cervical lymph node dissection.

cases were categorized as low grade for survival comparisons. The results showed significant differences in OS, disease-specific survival, distant metastasis-free survival, and local recurrence-free survival [170]. Nigam *et al.* evaluated prognosis based on pathological findings and calcitonin doubling time. They also found that cases showing tumor necrosis, mitotic rate ≥ 5 per 2 mm², or Ki-67 index $\geq 5\%$ were classified as high grade and were associated with significantly poorer prognosis [171].

Note 4-2: Tumor markers and dynamic prognostic factors in postoperative follow-up of MTC

Calcitonin and CEA represent excellent tumor markers for MTC [172]. If normal levels of calcitonin and CEA are observed postoperatively, biochemical cure is considered to have been achieved. Cases in which calcitonin or CEA does not normalize are classified as showing biochemical non-cure, strongly suggesting the presence of residual parafollicular cells producing calcitonin. Markers that initially normalize but later rise again indicate biochemical recurrence. In the event of biochemical recurrence, imaging studies should be con-

ducted to confirm structural recurrence. CT and MRI should be used to examine the neck, chest, and liver. Bone scans or whole-body MRI should only be considered for patients in whom bone metastases are suspected. Comprehensive examinations should be performed using multiple tests, but clear evidence on the optimal combinations remains lacking. On the other hand, in MTC, biochemical recurrence does not always equate to the emergence of structural recurrence [164]. Because calcitonin is a highly sensitive marker, instances can arise in which biochemical non-remission or recurrence are not revealed as clear sites of recurrence on imaging. In asymptomatic cases, immediate intervention is inadvisable; instead, measurement of calcitonin every 6–12 months is recommended as follow-up [173].

As a dynamic factor for predicting disease progression during follow-up, Miyauchi *et al.* demonstrated that calcitonin doubling time (Ct-DT) precisely reflects the tumor growth rate. Patients with a Ct-DT <0.5 years all died within 3 years, indicating poor prognosis (refer to Note 2-4 for the method of calculating doubling time) [168, 174]. However, tumor growth rates are not

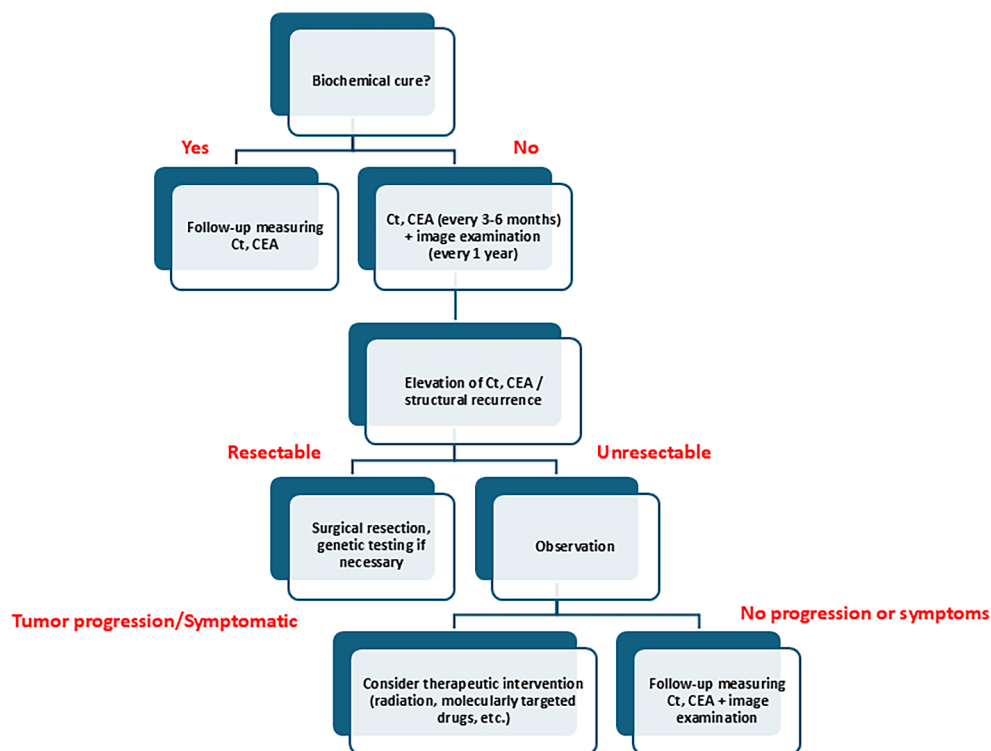


Fig. 7 Clinical algorithm 4-2. Postoperative surveillance for MTC
Ct: calcitonin.

necessarily constant. In a long-term follow-up study comparing Ct-DT in early and late stages over more than a decade, Miyauchi *et al.* reported that Ct-DT extended over time in many cases. This suggests that the tumor growth rate decreased during follow-up. Conversely, some cases of MTC, particularly sporadic types, may exhibit rapid tumor growth [175].

Note 4-3: RET genetic testing in the management of MTC

1) Hereditary MTC and RET gene mutations

MTC is a rare form of thyroid cancer, accounting for approximately 1–5% of cases. About 40% of MTC cases are hereditary, occurring as part of multiple endocrine neoplasia type 2 (MEN2). MEN2 is an autosomal dominant genetic disorder and is classified into types 2A and 2B. In type 2A, family members commonly have a history of MTC or pheochromocytoma. Eliciting a detailed family history from patients with MTC is thus crucial. However, one report indicated that 16% of seemingly sporadic MTC cases exhibited *RET* gene mutations [176], preventing diagnosis of hereditary MTC based solely on family history. Genetic testing is essential to definitively diagnose MEN2. The *RET* gene is responsible for MEN2 as an oncogene located on the long arm of chromosome 10 (10q11). Mutations associated with MEN2A have been confirmed in exons 6, 8, 10, 11, 13,

14, and 15, while MEN2B mutations are found in exon 16. Table 9 shows the mutation sites in *RET* and their association with MEN2 subtypes, and Table 10 shows the characteristic co-existing conditions seen in MEN2 [177].

2) Genetic testing in patients with MTC

In Japan, genetic testing for the *RET* gene is covered by public health insurance for patients diagnosed with MTC. Genetic testing for *RET* is necessary in all MTC patients prior to surgery, to confirm whether the MTC is hereditary. Hereditary MTC tends to be bilateral, so total thyroidectomy is mandatory regardless of tumor size or lymph node involvement. In addition, checking for pheochromocytoma before surgery is essential in cases of hereditary MTC, since this tumor often coexists with MEN2. If pheochromocytoma is present, surgery for that tumor should be prioritized to avoid triggering intraoperative hypertensive crisis. Table 11 shows the prevalence of pheochromocytoma in MEN2 based on data from the Japanese MEN Consortium [178].

Ideally, genetic counseling should be available at the time genetic testing is conducted, but in facilities where this is not possible, physicians with a knowledge of hereditary MTC and genetic testing can still provide basic explanations about the disease and genetic tests to the patients and obtain informed consent. If a *RET* mutation is detected, further genetic counseling and carrier

Table 9 *RET* gene mutations and classification of MEN2

Classification & site of domain	Extracellular cysteine-rich domain									Intracellular tyrosine kinase domain 1			Intracellular tyrosine kinase domain 2			
Codon	533	609	611	618	620	630	631	634*	666	768	790	804	883*	891	912	918**
Exon	8		10				11			13		14	15			16
MEN2 classification	MEN 2A												MEN 2B	MEN 2A		MEN 2B

American Thyroid Association (ATA) 2015 risk category: high*; highest**

MEN2: multiple endocrine neoplasia type 2.

Table 10 Prevalence of typical manifestations of MEN2

MEN2A 95%				MEN2B 5%
Classical MEN2A	MEN2A and CLA	MEN2A and HD	FMTC	MTC 100%
MTC 90%	MTC 95%	MTC 80%	No PHEO or PHPT	PHEO 50%
PHEO 30%	PHEO 50%	PHEO 20%		Ganglioneuroma 100%
PHPT 10%	PHPT 15%	PHPT 5%		Marfanoid habitus 70%
				Corneal nerve hypertrophy 45%
				Alacrimia 40%

MEN: multiple endocrine neoplasia; MTC: medullary thyroid carcinoma; PHEO: pheochromocytoma; PHPT: primary hyperparathyroidism.

Table 11 Penetration of pheochromocytoma in Japanese MEN2 patients

ATA 2015 risk category	Alteration site (codon)	Pheochromocytoma yes/no	Penetration of pheochromocytoma (%)
Highest	918	13/5	72.2
High	634	110/68	61.8
Moderate	609	1/5	16.7
	610	1/0	100
	611	4/20	16.7
	618	8/60	11.8
	620	5/34	12.8
	630	0/11	0
	768	1/18	5.3
	778	0/1	0
	790	0/1	0
	804	0/12	0
	891	0/10	0

diagnosis for family members should be conducted at a facility equipped to provide psychological support to both the patient and their family.

3) Genetic testing for relatives of patients with hereditary MTC

In Japan, *RET* genetic testing for unaffected relatives of patients with hereditary MEN2 MTC is conducted as a

self-funded service. For families with confirmed mutations, testing can be focused on the relevant exon. However, since this is predictive testing, individuals must decide whether to undergo testing after receiving genetic counseling from specialists such as clinical geneticists or genetic counselors.

Note 4-4: Screening for relatives of patients diagnosed with hereditary MTC and prophylactic (pre-symptomatic, pre-clinical) total thyroidectomy for asymptomatic RET mutation carriers

For relatives of patients diagnosed with hereditary MTC, *RET* genetic testing is recommended. However, *RET* genetic testing for asymptomatic individuals is not covered by public health insurance in Japan, and the environment is not fully prepared to handle issues such as future life insurance coverage for those found to be *RET* mutation carriers. If individuals choose not to undergo genetic testing, alternative screening options such as neck palpation, ultrasound screening of the neck, and calcitonin measurement can be performed on a self-funded basis.

Prophylactic thyroidectomy for *RET* mutation carriers was reported by Skinner *et al.* in 2005 [179]. Based on such reports, the ATA published guidelines in 2009, with an updated version released in 2015 [180]. For the highest-risk group (exon 18, codon 918 mutation), prophylactic thyroidectomy is recommended within the first month or first year of life. For the high-risk group (codon 634, codon 883 mutations), prophylactic thyroidectomy is recommended by 5 years old, based primarily on calcitonin levels. For patients in the moderate-risk group, prophylactic thyroidectomy is recommended when calcitonin levels rise or long-term observation is not desired. Although described as “prophylactic”, most reports on pediatric prophylactic thyroidectomy from abroad have included clinical cancers. The ATA guidelines define “prophylactic thyroidectomy” as removal of the thyroid before MTC develops or while still clinically undetectable and confined to the thyroid. Thyroidectomy for T1aN0 MTC classified could thus be considered sufficiently “prophylactic”. In fact, Beressi *et al.* reported that tumor size less than 1 cm is a factor in achieving biochemical cure [181], and postoperative biochemical cure is considered highly likely in such cases. Kihara *et al.* reported on MEN2 patients who underwent prophylactic thyroidectomy at the time of showing a positive result from a calcium stimulation test. Patients ranged in age from 8 to 30 years in the high-risk group and from 13 to 58 years in the moderate-risk group, all exceeding the recommended ages for prophylactic thyroidectomy set by the ATA. Since no recurrences were observed in any patients, even surgeries performed beyond the recommended age, as long as they are timed with a positive calcium stimulation test, may still lead to favorable outcomes [182].

The benefit of prophylactic thyroidectomy in children lies in achieving biochemical cure *via* total thyroidectomy while the patient is asymptomatic or in the stage of C-cell hyperplasia. On the other hand, a downside is the

potential for surgical complications. Reports from the Netherlands and Japan have documented surgical complications associated with prophylactic thyroidectomy among pediatric *RET* mutation carriers. In the Netherlands, the rate of permanent hypoparathyroidism was 20%, and the rate of recurrent laryngeal nerve injury was 4.5% (one transient case, one permanent case) [183]. In Japan, 33% of cases showed permanent hypoparathyroidism, 17% experienced transient recurrent laryngeal nerve paralysis, and 67% had some form of complication [184]. The report from the Netherlands noted a particularly high complication rate for surgeries performed on children under 3 years old. When performing prophylactic surgery, thorough explanation of potential complications and obtaining parental consent is thus essential.

CQ4-1.

Is lobectomy recommended for unilateral sporadic MTC?

Recommendation statement

Lobectomy is recommended for unilateral sporadic MTC.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 89% (re-vote)

Outcomes considered

- Treatment prognosis
- Biochemical cure rate
- Surgical complications
- Health status from the patient’s perspective

Evidence

- Few reports have examined the extent of resection limited to sporadic MTC, with one non-randomized controlled trial and five retrospective case-collection studies.
- No reports showed a statistical difference in OS.
- No difference in 5-year recurrence-free survival was seen between total and non-total thyroidectomy groups.
- No reports revealed a preference for total resection regarding biochemical cure.
- Both recurrent nerve injury and hypoparathyroidism were more frequent in the total thyroidectomy group.
- With sporadic MTC, the probability of bilateral lesions was less than 3% if the tumor was mono-focal preoperatively.
- The likelihood of bilateral disease increases to 8.3% if the tumor is classified as T3a, and to more than 10% for T4.
- No studies have examined health status from the patient’s perspective in MTC.

Summary and discussion of the literature

Six reports examined the extent of resection for

sporadic MTC compared to total resection. Three reports set the outcome as OS. No statistical difference in survival rate was found in any of those reports. However, it should be noted that definitions of survival rate differed in each report. Pillarisetty *et al.* reported a follow-up of 3.8 years and no deaths with any extension of thyroidectomy [185]. According to Zhang *et al.*, the 5-year cumulative survival rate was 97.4% in the total thyroidectomy group and 92.8% in the non-total thyroidectomy group ($p = 0.314$), showing no significant difference [186].

Two studies dealt with issues of recurrence. Kihara *et al.* compared the prognosis of hereditary and sporadic MTC in terms of 15-year DFS. As for sporadic disease, subtotal thyroidectomy was performed for unilateral disease and total thyroidectomy for bilateral disease. As a result, 15-year DFS was 100% in the hereditary group and 90% in the sporadic group [187]. Zhang *et al.* compared the extent of thyroidectomy in sporadic cases and found no significant difference in recurrence-free survival (RFS) between hemithyroidectomy and total thyroidectomy. The 5-year RFS was 88.9% in the total resection group and 82.5% in the non-total resection group ($p = 0.409$), showing no significant difference. Risk factors for recurrence were biochemical recurrence, tumor diameter ≥ 4 cm, and metastasis to lateral cervical lymph nodes [186].

Four studies in the literature determined the outcomes as biochemical cure of abnormal calcitonin. None of those studies showed any difference according to the extent of thyroidectomy. However, definitions of biochemical cure differed between studies. Some studies evaluated postoperative calcitonin levels, while others used calcitonin levels after stimulation by pentagastrin and calcium or calcium alone. Miyauchi *et al.* identified T1-2, lateral lymph node dissection, and pathological node-negative status as factors for achieving biochemical cure [185, 186, 188, 189].

Two reports used adverse events as an outcome measure. The frequency of hypoparathyroidism was 40.7% with total thyroidectomy and 0% with non-total thyroidectomy [186]. The frequency of recurrent nerve injury was 58.3% for total resection and 1.3% for non-total resection [189].

A retrospective analysis of the possibility of multiple sporadic MTCs in patients undergoing total thyroidectomy was reported [190]. If a solitary lesion was present in one lobe preoperatively, the proportion of bilateral lesions found postoperatively was 2.8%. In cases where multiple lesions were present in one lobe preoperatively, the percentage of bilateral lesions increased to 21.6%. Concerning tumor size, the likelihood of bilateral involvement was: T0-T1a, 6.5%; T1b, 2%; T2, 0%; T3, 8.2%; T4a, 11.5%; and T4b, 18.2%. A trend was thus

seen towards a higher likelihood of bilateral disease as tumor diameter increased.

In summary, no evidence suggested better survival, recurrence, or biochemical cure with total thyroidectomy compared to lobectomy for sporadic MTC. However, a slight possibility of contralateral involvement is present even in patients with a single, unilateral lesion, particularly in cases of T4 and above, reaching as high as 10% or more. However, whether the presence of residual contralateral microlesions influences prognosis is unclear. In addition, MTCs originate from parafollicular cells, which are not indicated for RAI therapy. Lobectomy is therefore recommended for sporadic unilateral MTC.

CQ 4-2.

Is unilateral modified lymph node neck dissection recommended in patients with sporadic MTC?

Recommendation statement

Prophylactic unilateral modified lymph node neck dissection is not recommended in patients with sporadic MTC and clinical N0 status.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 78%

Outcome considered

- Treatment prognosis
- Rate of biochemical cure
- Surgical adverse events
- Health status from the patient's perspective

Evidence

- All studies comparing cN0 MTC with or without prophylactic lateral lymph node dissection were retrospective studies.
- No significant differences were seen in recurrence rate, disease-specific survival, OS, or biochemical cure rate according to the presence or absence of prophylactic lateral lymph node dissection.
- Studies comparing occurrences of surgical complications (hypoparathyroidism or recurrent laryngeal nerve palsy) revealed that patients with only central compartment dissection had lower complication rates than those with prophylactic lateral lymph node dissection.
- No significant differences in recurrence rate, disease-specific survival, OS, or biochemical cure rate were observed between patients with or without prophylactic lateral lymph node dissection.
- No health status studies based on the patient's perspective have been reported.

Summary and discussion of the literature

Three studies compared surgical outcomes for cN0 MTC with or without prophylactic lateral lymph node dissection, and all were retrospective. Yamashita *et al.* compared the prognostic value of prophylactic lateral

neck lymph nodes in patients with 110 sporadic and hereditary MTCs diagnosed as cN0 on preoperative imaging. Overall recurrence rates with and without prophylactic dissection were 39% and 20% ($p = 0.46$), respectively, and local recurrence rates with and without prophylactic dissection were 22% and 7.6% ($p = 0.08$), respectively. The group with prophylactic dissection showed worse recurrence rates. However, only 18 cases were included in the prophylactic dissection group, which likely impacted the statistical significance of the results. Five-year OS rates with and without prophylactic dissection were 31% and 43% ($p = 0.52$), showing no difference. The group without prophylactic dissection tended to have more cases up to T2 and lower preoperative calcitonin levels than the group with prophylactic dissection. The reasons for the considerably lower survival rate are unclear [191].

Spanheimer *et al.* also reported prognosis for 316 cases of MTC from 1986 to 2017. Eighty-nine patients with preoperative calcitonin levels ≥ 200 pg/mL and cN0 were analyzed. The presence or absence of prophylactic lateral lymph node dissection determined the prognosis. OS rates at 10 years after surgery with and without prophylactic dissection were 82% and 90% ($p = 0.6$), disease-specific survival rates were 86% and 93% ($p = 0.53$), cumulative incidences of recurrence were 20.9% and 30.4% ($p = 0.46$), and cumulative incidences of distant recurrence were 18.3% and 18.4% ($p = 0.97$), respectively. They concluded that prophylactic lateral lymph node dissection did not improve prognosis [192].

Pena *et al.* analyzed the prognosis of 66 cN0 sporadic MTC cases based on the presence or absence of lateral lymph node dissection. Local recurrence-free rates with or without dissection were 100% and 98% ($p > 0.999$), 5-year OS rates were 100% vs. 84% ($p = 0.159$), and biochemical cure rates were 85% and 82% ($p > 0.999$), respectively. No differences were apparent between groups. However, median preoperative calcitonin levels were 1,243 pg/mL and 714 pg/mL in patients with and without dissection, respectively, representing a significant difference ($p = 0.016$) [193].

A European database was used to study adverse events [194]. According to that study, hypoparathyroidism, recurrent nerve palsy, and postoperative hemorrhage occurred postoperatively in 26.2%, 13.7%, and 2.6% of patients with MTC. In terms of hypoparathyroidism, odds ratios (ORs) for central dissection, central + unilateral dissection, and central + bilateral dissection compared to no dissection were 2.20 (95%CI 1.04–4.67), 2.78 (1.20–6.43), and 2.83 (1.13–7.05), respectively. The frequency was significantly higher than cases in which dissection was not performed ($p = 0.040$, 0.017, and 0.026, respectively). In cases with recurrent nerve palsy,

ORs for central dissection and central plus lateral dissection compared to no dissection were 2.82 (95%CI 0.76–10.39) and 4.04 (95%CI 1.12–14.58), respectively. A significant increase in risk was observed when lateral neck dissection was performed ($p = 0.033$).

Chapter 5. Poorly differentiated thyroid carcinoma

Note 5-1. Poorly differentiated thyroid carcinoma (PDTC)

PDTC is a rare malignant tumor derived from the follicular epithelium, demonstrating intermediate morphological and biological characteristics between well-differentiated carcinoma (papillary and follicular carcinomas) and anaplastic carcinoma. The concept of PDTC was initially proposed by Sakamoto *et al.* in 1983, followed by a report from Carcangiu *et al.* on insular carcinoma in 1984 and the Turin criteria for PDTC in 2007, which further organized the disease concept [195–197]. The WHO Classification of Tumours, 5th edition in 2022 adopted the Turin criteria for PDTC, while the Japanese General Rules for the Description of Thyroid Cancer (8th edition in 2019 and 9th edition in 2023) utilized diagnostic criteria based on the WHO Classification, 3rd edition in 2004. The pathological diagnosis of PDTC thus exhibits slight differences between international and domestic practices (Table 12).

The diagnosis of PDTC is primarily based on pathological examination of surgical specimens. While PDTC can be estimated from preoperative FNAC, differentiation from follicular tumors is often challenging. Macroscopically, PDTC shows invasive growth. The tumor may present with well-defined borders and a fibrous capsule, but at least capsular or vascular invasion is typically present. The characteristic histological architecture is predominantly solid, trabecular, or insular, often accompanied by coagulative necrosis within the tumor. The frequency of mitotic figures is higher than seen in differentiated carcinomas, at ≥ 3 per 2 mm². Typical nuclear findings of papillary carcinoma are not observed. As a criterion of the Sloan–Kettering classification, a definition has been proposed whereby carcinoma is classified as poorly differentiated if ≥ 5 mitotic figures are seen per 2 mm² or tumor necrosis is present, regardless of the histological architecture or nuclear findings. However, in the WHO Classification of Tumours, 5th edition, thyroid cancers that meet this criterion but display a histological architecture corresponding to differentiated carcinoma have been newly defined as differentiated high-grade thyroid carcinoma [198].

PDTC can arise either *de novo* or through multistep carcinogenesis from differentiated carcinoma [199]. This

Table 12 Diagnostic criteria for poorly differentiated thyroid carcinoma

	Japanese General Rules for the Description of Thyroid Cancer, 9th edition (2023)	WHO Classification of Tumours, 5th edition (2022) /Turin criteria	Memorial Sloan-Kettering (MSKCC) classification
Histological architecture	Solid, trabecular, or insular components constitute >50% of the tumor.	Solid, trabecular, or insular structures. No quantitative criteria.	No criteria
Mitotic figures, coagulative necrosis, convoluted nuclei	Not required	One of the following is required: 1. Mitotic figures: three or more per 2 mm ² 2. Coagulative necrosis 3. Convoluted nuclei	One of the following is required: 1. Mitotic figures: five or more per 2 mm ² 2. Coagulative necrosis
Nuclear findings	No nuclear findings characteristic of papillary carcinoma.	No nuclear findings characteristic of papillary carcinoma.	No criteria

pathology often includes follicular structures, and the frequency of *RAS* mutations (18–27%) is higher than that of *BRAF* mutations (0–13%). This suggests that many cases of PDTC likely originate from follicular tumors [199, 200].

In Japan, PDTC is rare, accounting for only 0.7% of all thyroid cancers. Adopting the Turin criteria, this frequency decreases further to 0.3% [201]. The 10-year DFS rate for PDTC ranges from 48% to 66%, while the 10-year CSS rate ranges from 44% to 88%, indicating a poorer prognosis compared to differentiated carcinoma. For PDTC that meets the Turin criteria, both DFS and CSS are further reduced [201–203].

CQ 5-1.

Is ablation or adjuvant therapy using RAI recommended for cases diagnosed as PDTC?

Recommendation statement

For cases diagnosed as PDTC, ablation or adjuvant therapy using RAI can be offered.

Certainty of evidence: D

Strength of recommendation: Weak; **Consensus rate:** 100%

Outcomes considered

- Treatment prognosis
- Success rate of ablation
- Health status from the patient's perspective

Evidence

- No studies have directly compared RAI administration and non-administration groups in a large number of cases by matching background characteristics.
- Success rates for ablation of PDTC without distant metastasis have been reported as 61–100%.
- No studies have reported health status from the patient's perspective.

Summary and discussion of the literature

A few studies have been published regarding RAI

administration for the purpose of ablation or adjuvant therapy after surgery for PDTC, but all have been retrospective and the cases analyzed underwent miscellaneous treatments. De Silva *et al.* investigated 38 PDTCs (TgAb-negative) without distant metastasis. All underwent total thyroidectomy followed by RAI ablation (median, 8.363 GBq), and reported that 61% of patients showed a post-therapy Tg ≤1 ng/mL (cases with successful ablation) [204]. Cases with successful ablation were more likely to show negative stumps and N0 than non-successful cases and DFS and CSS rates were significantly better. However, these criteria cannot be applied for TgAb-positive cases and RAI administration cases were not directly compared with non-administration cases. On the other hand, Thiagarajan *et al.* reported that when ablation success was defined as uptake <0.2% and Tg <2 ng/mL, all 20 cases were judged as showing ablation success [205]. However, these results cannot be used as grounds to claim that ablation improves patient prognosis. All other studies analyzed cases that underwent various therapies, and according to Lee *et al.*, cases treated using adjuvant therapies such as RAI and extra-beam radiotherapy tended to show better prognosis than those that did not, but no significant difference could be established between groups [206]. Yu *et al.* showed that all 6 patients with PDTC who underwent adjuvant RAI administration were alive during follow-up (length unknown) [207].

Taken together, the possibility that RAI administration for ablation or adjuvant therapy in postoperative PDTC patients reduces the recurrence rate and improves prognosis cannot be denied. Further, if recurrence develops thereafter, the lesion can immediately be regarded as RAI-refractory and physicians can move on to the next treatment strategy, which is beneficial. RAI administration for the purpose of ablation or adjuvant therapy is thus offered from the standpoint of multidisciplinary

therapy for diseases with poor prognosis.

CQ 5-2.

Is RAI therapy recommended for distant metastasis of PDTC?

Recommendation statement

For distant metastasis of PDTC, RAI therapy can be offered depending on metastasized organs and the situation of metastasis.

Certainty of evidence: D

Strength of recommendation: Weak; **Consensus rate:** 100%

Outcomes considered

- Response rate
- Treatment prognosis
- Health status from the patient's perspective

Evidence

- The incidence of RAI-avid distant metastasis of PDTC is reported as 60–82.4%.
- RAI-avid distant recurrence reportedly shows complete response (CR) at a rate of 33–88%.
- No comparative studies have been published regarding whether distant metastatic lesions are RAI-avid or -refractory or whether RAI therapy performed for metastatic lesions affects patient prognosis.
- No studies have been published about health status from the patient's perspective.

Summary and discussion of the literature

Table 13 summarizes reports regarding RAI therapy for metastatic lesions of PDTC [205, 208–210]. All of these were retrospective studies. The incidence of distant recurrences being RAI-avid varied significantly according to studies, reaching as high as 82.4% [210]. Moreover, RAI-avid distant recurrences were reported to show CR at a high rate [205]. However, RAI uptake of metastatic lesions does not imply that RAI administration is significantly effective for lesions or contributes to the prolongation of patient survival. In clinical settings, physicians often encounter cases showing findings suggestive of disease progression, such as enlargement of metastatic lesions and/or Tg elevation, despite metastatic lesions showing very strong RAI uptake. Even in a report showing a high 33% rate of attaining CR, the period of disease non-progression for M1 cases was a short 25 months, and the 3-year disease non-progression rate was low, at 69% [205]. This indicates that the prognosis of PDTC is not good on the whole. These findings are attributed to progression of other RAI-refractory metastatic lesions or new appearance of RAI-refractory lesions. Further, in cases with coexistence of both poorly and well-differentiated carcinoma, RAI may only exert a substantial impact on well-differentiated metastases.

At present, at least in principle, a standard treatment

(RAI therapy) should be preferred, and if this proves ineffective, administration of molecularly targeted agents should be considered. Although it remains uncertain whether RAI therapy truly provides a therapeutic benefit, distant metastatic lesions of PDTC are frequently RAI-avid. For these, RAI administration should be offered as a first-line treatment. However, whether further RAI administration is performed should be carefully discussed based on careful tracing of changes in size and shape of metastatic lesions and in Tg values, instead of repeating RAI treatment excursively.

In cases showing vertebral metastasis reaching to the axis or lung metastasis already causing dyspnea, patient QOL may be in danger of significant deterioration with temporary levothyroxine (LT4) withdrawal resulting in progression of recurrent tumors. For such cases, appropriate treatment strategies must be considered on an individual basis (see CQ8-6).

Chapter 6. Anaplastic thyroid carcinoma (ATC)

Note 6-1. Overview of treatment for ATC

According to the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC TNM) classification, the staging of ATC is defined by the presence of extrathyroidal extension, lymph node involvement, and distant metastasis, which helps estimate prognosis and evaluate the extent of disease. The prognostic index (PI) developed in Japan can be assessed before treatment begins and effectively reflects patient survival outcomes [211, 212]. Patients with a low PI should receive aggressive treatment to extend survival, while those with a high PI may benefit more from best supportive care focused on quality of survival.

No standard treatment has been established for ATC. For patients diagnosed with ATC, providing supportive care from the outset is crucial, regardless of whether aggressive treatment is pursued. Historically, a multidisciplinary approach involving surgical resection, adequate external beam radiation (40–60 Gy or more), and multi-agent chemotherapy centered around doxorubicin has occasionally yielded long-term survival. However, most ATC cases are Stage IVB or IVC and curative resection is rare.

In Japan, the potential of weekly paclitaxel (wPTX) as induction chemotherapy has been explored through a multi-institutional prospective clinical trial (ATCCJ-PTX-P2). The results suggest that wPTX might extend survival if subsequent curative resection proves feasible in Stage IVB patients (CQ6-2); however, this is not covered by insurance [213]. In 2015, the molecularly

Table 13 RAI therapy for distant recurrences of poorly differentiated carcinomas

Authors	Subject aggregation Number of subjects	Follow-up	Outcomes	Consideration
Ibrahimipasic <i>et al.</i> 2013 [208]	Twenty-seven cases of poorly differentiated carcinoma as defined by MSKCC with gross invasion	Median, 57 months [1–197 months]	1) Lung metastasis in 7 of the 10 cases were RAI-avid. 2) Five-year overall and cause-specific survival rates were 47% and 49%, respectively.	Although the relationship between RAI-avidity and prognosis was not discussed, the incidence of RAI-avid metastatic lesions was high
Ibrahimipasic <i>et al.</i> 2014 [209]	Ninety-one cases of poorly differentiated carcinoma as defined by MSKCC, with 24 cases (26%) positive for distant metastasis	Median, 50 months [1–215 months]	1) Of 24 patients with distant metastasis, 17 (70%) were RAI-avid. 2) Five-year overall survival rate 62%, cause-specific survival rate 66%.	Although the relationship between RAI-avidity and prognosis was not discussed, incidence of RAI-avid metastatic lesions was high
De La Fouchardiere <i>et al.</i> [210]	Poorly differentiated carcinoma 104 cases	Median, 59.3 months [29.5–90.7 months]	1) RAI administered for 99 cases (95.2%). Thirty-four were M1, of which 28 (82.4%) were detected after postoperative RAI administration. 2) Thirty-seven obtained remission in initial therapy, 63 showed persistent disease, 4 were unknown. 3) Sixty-two and 14 received second and third bouts of RAI therapy, respectively. Fifty-two were RAI-refractory. 4) <i>TERT</i> mutation-positive cases were more likely to be RAI-refractory, but this was unrelated to survival rates. 5) Five-year overall survival and recurrence-free survival were 72.8% and 45.3%, respectively.	Although metastatic lesions were frequently RAI-avid, whether this contributes to improvement of prognosis remains unknown
Thiagarajan <i>et al.</i> 2020 [205]	Poorly differentiated carcinoma 35 cases. All underwent surgery and RAI therapy (median, 220 mCi; range, 40–1140 mCi). Seventy one were M1.	Median, 33 months; range, 6–64 months	1) Three-year non-progression rate, 69%. Local non-curativity, M1, age ≥ 45 years as predictors of poor prognosis. 2) Six (33%) of 18 patients with lung metastasis/recurrence achieved CR with RAI administration. 3) Median disease non-progression period: 25 months in M1 cases, 37 months in M0 patients.	RAI is often very effective for distant metastasis, but whether and how this contributes to prolonging prognosis of patients remains unknown.

targeted drug lenvatinib, primarily a vascular endothelial growth factor receptor (VEGF-R) inhibitor, was approved for use in ATC when unresectable target lesions are present. The HOPE trial, a multi-institutional prospective clinical trial in Japan, showed a response rate to lenvatinib of 11.9% in unresectable ATC, with a 1-year overall survival rate of 11.9%, which was not considered sufficient [214].

Reports from the MD Anderson Cancer Center in the United States indicate that recent treatment outcomes for ATC have improved markedly [215]. The 1-year overall survival rate for 227 patients treated between 2000 and 2013 was 35%, and the 2-year survival rate was 18%. In

contrast, for 152 patients treated between 2017 and 2019, the 1- and 2-year survival rates were 59% and 42%, respectively (HR 0.50, 95%CI 0.38–0.67). The advent of BRAF/MEK inhibitors (with or without immune checkpoint inhibitors) has been a game changer. Recent reports from the same institution have indicated that preoperative treatment with BRAF/MEK inhibitors (with or without immune checkpoint inhibitors) in *BRAF* V600E mutation-positive cases resulted in a 1-year overall survival rate of 94% after curative resection, with many cases showing a reduction in the extent of resection [216].

As BRAF/MEK inhibitors have recently been approved for use in Japan, early genetic testing through

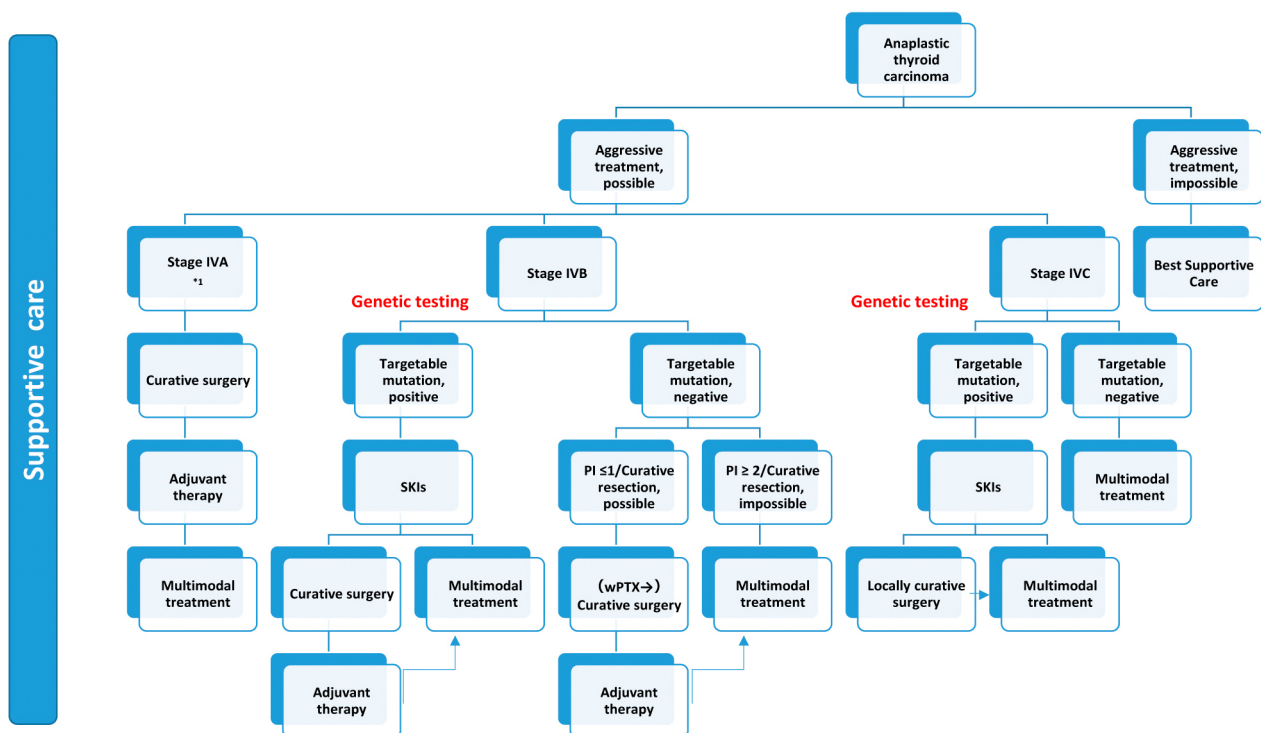


Fig. 8 Clinical algorithm 6-1. Management of anaplastic thyroid carcinoma (ATC)

- Currently, no standard treatment has been devised for ATC. Treatment goals should be flexibly set based on patient performance status, extent of disease (Stage), and prognostic factors such as prognostic index (PI), with decisions made through shared decision-making.
- Consistent supportive care from the time of diagnosis is essential.
- For cases amenable to curative resection, proceeding with radical surgery is generally recommended.
- During the waiting period for treatment (e.g., awaiting genetic test results), weekly paclitaxel (wPTX) can be considered (although this is not covered by insurance). Multitargeted molecular inhibitors (such as lenvatinib) carry risks of delayed wound healing and bleeding, so preoperative use of these agents is not recommended.

*1 Genetic testing as needed

Adjuvant therapy: radiation therapy, wPTX (off-label)

Multimodal treatment: selective kinase inhibitors (SKIs), in addition to radiation therapy, wPTX (off-label), multi-targeted tyrosine kinase inhibitor (lenvatinib), palliative surgery, etc.

PI: prognostic index; number of applicable items out of the following 4 risk factors: 1) acute worsening of symptoms within 1 month; 2) tumor size over 5 cm; 3) white blood cell count over 10,000/m³; and 4) presence of distant metastasis.

tissue biopsy to assess *BRAF* mutations and guide treatment decisions will become increasingly essential for the management of ATC.

Clinical algorithm 6-1. Management of ATC (Fig. 8)

CQ 6-1.

Is postoperative treatment recommended for cases where incidental ATC is diagnosed after radical surgery?

Recommendation statement

Postoperative treatment is recommended for patients in whom a small amount of incidental ATC is identified in postoperative pathology.

Certainty of evidence: D

Strength of recommendation: Weak; **Consensus rate:**

89%

Outcomes considered

- Treatment outcomes
- Adverse events
- Patient-reported outcomes

Evidence

- Research focusing on incidental ATC remains limited, and all studies have been retrospective.
- The prognosis of incidental ATC is generally better compared to typical ATC, but approximately half of patients still die from the primary disease.
- Studies comparing treatment outcomes between cases with and without adjuvant therapy for incidental ATC after radical surgery are limited. A study by the ATC Research Consortium of Japan (ATCCJ) showed a

tendency toward better outcomes for groups receiving additional radiotherapy or chemoradiotherapy compared to radical surgery alone, but statistical significance was not achieved.

- No research reports have provided patient-reported outcomes.

Summary and discussion of the literature

Incidental ATC components are rarely found in resected specimens. Such findings are more common in women, and the associated differentiated carcinomas are mostly PTCs. Compared to typical ATC, incidental ATC is usually smaller, with less extrathyroidal extension, fewer distant metastases, and significantly better prognosis. According to studies by the ATCCJ, the 1-year OS rate is 71.8% and the 2-year OS rate is 58.3% [212, 217–220].

Regarding adjuvant therapy after radical surgery, reports from the ATCCJ showed better outcomes for an additional radiation therapy group (7 cases, 87.5%) and a chemoradiotherapy group (5 cases, 100%) compared to radical surgery alone (6 cases; 1-year disease-specific survival rate, 50%). However, no significant differences were observed [219].

Evidence for the effectiveness and safety of adjuvant treatment after radical surgery for incidental ATC is limited, and prospective comparative trials are needed in future. Nevertheless, additional treatment may improve prognosis, similar to Stage IVA cases after R0/1 resection, and performing such treatment based on the overall condition and preferences of the patient is recommended. No evidence supports the preventive use of multi-kinase inhibitors in the absence of target lesions.

CQ 6-2.

Is neoadjuvant therapy recommended for ATC being considered for radical resection?

Recommendation statement

In ATC cases for which radical resection is being considered, neoadjuvant therapy based on genetic test results is recommended:

1. For *BRAF* mutation-positive cases, *BRAF*/*MEK* inhibitors should be used.

Certainty of evidence: D

Strength of recommendation: Weak; **Consensus rate:** 89%

2. For *BRAF* mutation-negative cases, wPTX is recommended, but is not covered by public insurance in Japan.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 89%

Outcomes considered

- Treatment outcomes

- Adverse events
- Patient-reported outcomes

Evidence

- Reports on neoadjuvant therapy for ATC remain limited and the evidence is not yet sufficient.
- According to a retrospective report from MD Anderson Cancer Center, neoadjuvant *BRAF*/*MEK* inhibitors (with or without immune checkpoint inhibitors) for *BRAF* V600E mutation-positive ATC showed a 1-year overall survival rate of 94% and a 1-year progression-free survival rate of 84% among 32 patients who underwent radical resection, with many cases showing a reduced extent of resection.
- A retrospective report by Higashiyama *et al.* indicated that wPTX as induction therapy for Stage IVB ATC resulted in significantly better overall survival compared to cases that did not receive chemotherapy or that received other chemotherapies. Of these, four cases underwent radical resection after wPTX and survived 11–32 months.
- The effectiveness of wPTX has been evaluated in a prospective multi-center study led by the ATCCJ. Survival for the eight cases that underwent radical resection after wPTX was significantly longer compared to other cases. Although the incidence of adverse events was 98%, only 29% were Grade 3 or higher, and no cases required discontinuation of treatment due to adverse events.
- No consolidated reports have clarified the use of lenvatinib as a neoadjuvant therapy.
- No research reports have clarified patient-reported outcomes regarding health status.

Summary and discussion of the literature

1) Use of wPTX

The significance of wPTX as induction chemotherapy for ATC was first reported by Higashiyama *et al.* [221]. In nine Stage IVB cases, the response rate was 33% (CR in 1 case, partial response [PR] in 2 cases), and the overall survival rate for wPTX-treated cases was significantly better than for those who did not receive chemotherapy (50 cases, $p = 0.0213$) or who received other chemotherapies (24 cases, $p = 0.0467$). Four of the nine cases that received wPTX subsequently underwent radical resection and survived 11–32 months.

Following this, the ATCCJ conducted a physician-led multi-center phase II trial of wPTX [213]. Of the 56 registered cases, the completion rate for at least one course was 93% and adverse events occurred in 55 cases (98%) (*e.g.*, anemia in 77%, alopecia in 68%). However, Grade 3 or higher adverse events were limited to 16 cases (28%) (*e.g.*, neutropenia in 11%), and no cases required discontinuation of treatment due to adverse events. Median overall survival was 6.7 months, with a 6-month

survival rate of 54%. The response rate among the 42 cases with measurable disease was 21%, with a clinical benefit rate of 73% (PR in 21%, stable disease in 52%, PD in 19%). Median progression-free survival was 1.6 months. For the eight cases that underwent radical resection after wPTX, median survival was 7.6 months, significantly longer than the 5.4 months in other cases ($p = 0.018$).

Based on these results, wPTX for Stage IVB ATC may potentially extend survival if radical resection subsequently becomes feasible.

2) BRAF/MEK inhibitor combination therapy

According to reports from the MD Anderson Cancer Center, BRAF/MEK inhibitors were administered to six cases of *BRAF* V600E mutation-positive ATC that were initially unresectable, with some cases also receiving pembrolizumab. All cases subsequently underwent radical resection. The 6-month overall survival rate was 100%, and the 1-year survival rate was 83%, with a local control rate of 100% [222]. More recent data from the same institution indicated that BRAF/MEK inhibitors were administered for at least 1 month to 57 cases of *BRAF* V600E mutation-positive ATC (35% Stage IVB, 65% Stage IVC) between 2017 and 2021 (43 cases also received immune checkpoint inhibitors) [216]. Among these, 32 cases (neoadjuvant therapy group) underwent primary tumor resection after treatment, 12 cases (adjuvant therapy group) received BRAF/MEK inhibitors post-resection (nine cases underwent surgery at other institutions), and 13 cases (non-surgical group) did not undergo surgery (nine due to disease progression or insufficient efficacy, two due to poor performance status, two due to refusal). The 1-year overall survival rate for the neoadjuvant therapy group (median duration of treatment with BRAF/MEK inhibitors, 136 days) was 93.6%, with a progression-free survival rate of 84.4%. For the adjuvant therapy group, these rates were 74.1% and 50%, respectively, compared to rates of 38.5% and 15.4% for the non-surgical group. In the neoadjuvant therapy group, most cases showed reductions in the extent of resection (improvements in surgical morbidity and complexity scores), with nine cases that had initially been deemed unresectable becoming resectable post-treatment.

In summary, BRAF/MEK inhibitor combination therapy for *BRAF* V600E mutation-positive ATC may enable resection of previously unresectable cases and potentially improve survival outcomes. However, no comparative studies have included cases with radical resection as the initial approach.

CQ 6-3.

Is combined resection of other organs recommended

for ATC with extrathyroidal invasion?

Recommendation statement

For ATC with extrathyroidal invasion, combined resection of other organs to achieve complete resection is proposed.

Certainty of evidence: D

Strength of recommendation: Weak; **Consensus rate:** 89%

Outcomes considered

- Treatment outcomes
- Adverse events
- Patient-reported outcomes

Evidence

- Research on radical extended surgery for ATC with local invasion has been limited to retrospective studies.
- Machens *et al.* reported that among cases involving combined resection of adjacent organs including the trachea, larynx, and esophagus, R0/1 resections achieved better survival outcomes than R2 resections.
- Brown *et al.* reported on 16 cases of extended radical surgery without carotid artery invasion, noting that after an average follow-up of 4.8 years, 7 patients remained alive without recurrence. All surviving patients were able to resume oral intake.
- According to the study from the ATCCJ, 23 cases of Stage IVB ATC (as per AJCC/UICC 7th edition) that underwent extended radical resection showed survival outcomes comparable to 49 cases that underwent radical resection without extension. These outcomes were better than those of 72 cases that received palliative resection and 80 cases that did not undergo surgery. Among the cases with extended radical resection, 78% required permanent tracheostomy.
- No research concerning patient-reported outcomes has been reported.

Summary and discussion of the literature

Cases of ATC with successful local radical resection have traditionally been considered to show better survival outcomes than other cases. However, ATC without invasion to adjacent organs (Stage IVA) is rare, and most cases are Stage IVB with extrathyroidal invasion. Generally, in ATC, combined resection of the strap muscles, unilateral recurrent laryngeal nerve, tracheal surface, muscular layer of the esophagus, and internal jugular vein is considered acceptable. In contrast, cases with gross invasion into the carotid artery or prevertebral muscles are regarded as unresectable. Research reports on the outcomes of radical extended resection involving full-layer resection of the trachea/larynx, esophagus/pharynx, or sternotomy are scarce, and the few that have been published have been retrospective studies with a small number of cases.

According to Machens *et al.*, among cases that

underwent combined resection of adjacent organs including partial resection of the trachea, larynx, and esophagus, survival outcomes were better for R0/1 resections than for R2 resections [223]. Brown *et al.* reported on 16 cases of extended radical surgery without carotid artery invasion (12 laryngectomies, 4 resections of the trachea, 6 resections of the cervical esophagus, and 2 mediastinal surgeries with sternotomy). No cases showed local recurrences, with 7 patients remaining alive without recurrence after an average follow-up of 4.8 years, 6 cases with distant recurrence, 1 case with death from other causes, and 2 cases with unknown outcomes. All surviving patients were able to resume oral intake [224].

According to an analysis of the ATCCJ multi-center database in Japan, extended radical resection involving total resection of the trachea/larynx or esophagus/pharynx or mediastinal surgery with sternotomy was performed in 23 of 233 cases of Stage IVB anaplastic carcinoma. The 1-year disease-specific survival rate was 33%, comparable to the 41% survival rate of 49 cases that underwent radical resection without extension ($p = 0.94$) and better than the 15% survival rate of 72 cases that underwent palliative resection or the 10% survival rate of 80 cases that did not undergo surgery. In the extended radical resection group, the 1-year disease-specific survival rate was 50% for cases with a PI ≤ 1 , compared to 11% for cases with a PI ≥ 2 . In addition, 78% of cases with extended radical resection required permanent tracheostomy [225].

Based on these findings, full-layer resection of the trachea/larynx or esophagus/pharynx (with reconstruction as needed) may improve local control rates and potentially enhance survival outcomes for ATC with extrathyroidal invasion compared to palliative surgery or no surgery with multimodal treatment. However, the decision on taking this approach should be made with consideration of the overall condition, preferences, and potential complications of the patient, and based on prognostic predictions using indices such as PI.

As discussed in CQ 6-2, recent reports from the United States have shown favorable results for radical resection after BRAF/MEK inhibitor therapy (with or without immune checkpoint inhibitor therapy) for *BRAF* V600E mutation-positive ATC [216, 222, 226, 227]. These treatments have made previously unresectable cases resectable and may improve survival outcomes with safer and more reliable radical surgery.

CQ 6-4.

Is postoperative radiation therapy recommended for patients with ATC who have undergone successful radical resection?

Recommendation statement

Postoperative (chemo)radiotherapy is recommended for patients with ATC who have undergone successful radical resection (R0 resection).

Certainty of evidence: D

Strength of recommendation: Weak; **Consensus rate:** 100%

Outcomes considered

- Treatment outcomes
- Adverse events
- Patient-reported outcomes

Evidence

- Few studies have compared the treatment outcomes of postoperative radiotherapy for patients with ATC who have undergone R0 resection as compared to those who did not receive radiotherapy, and all such studies have been retrospective.
- According to a report from the ATCCJ, the addition of (chemo)radiotherapy did not significantly improve overall survival for Stage IVA patients, but did significantly improve overall survival for Stage IVB patients.
- Other retrospective analyses have shown that survival tended to be longer in the group receiving (chemo)radiotherapy after R0 resection compared to the group not receiving radiotherapy, although no statistical significance was demonstrated.
- A meta-analysis of 17 retrospective studies also indicated longer survival in the radiotherapy group after R0 resection compared to the non-treatment group, but the difference was not significant.
- No research reports have clarified adverse events or patient-reported outcomes.

Summary and discussion of the literature

According to a report from the ATCCJ involving 80 cases with R0 resection, among Stage IVA patients, the 1-year overall survival rate was 50% for 11 patients receiving postoperative chemoradiotherapy, and 67% for 9 patients receiving postoperative radiotherapy alone, both of which tended to be better than the 22% for 9 patients who did not receive any postoperative therapy. However, this difference was not significant. Conversely, in Stage IVB cases, the 1-year overall survival rate for 35 patients receiving postoperative chemoradiotherapy was 57%, higher than the 36% for 12 patients receiving postoperative radiotherapy alone and the 22% for 25 patients who did not receive any postoperative therapy. A significant difference was observed between the chemoradiotherapy group and the group with no additional treatment (Stage classification according to AJCC/UICC 7th edition) [212].

In a single-institution retrospective analysis from Korea, among cases with R0 resection, median survival for 31 patients receiving radiotherapy was 43.6 months,

compared to 25.9 months for 12 patients without radiotherapy, but this difference was not significant (HR 1.11, 95%CI 0.45–2.71; $p = 0.345$) [206]. A report using the National Cancer Database from the United States found that among 128 patients who received radiotherapy (with or without chemotherapy) after R0 resection, median survival was 17.5 months, compared to 11.0 months for 42 patients who did not receive radiotherapy, with no significant difference ($p = 0.36$) [228].

A meta-analysis conducted in 2016 using 17 retrospective studies found that postoperative radiotherapy significantly reduced mortality compared to surgery alone (HR 0.556, 95%CI 0.419–0.737; $p < 0.001$). However, when limited to the 102 cases with R0 resection, no significant difference was seen (HR 0.286, 95%CI 0.068–1.196; $p = 0.086$) [229].

Therefore, while studies on postoperative radiotherapy following R0 resection lack sufficient power to demonstrate statistical significance, radiotherapy may improve survival in ATC patients. The implementation of radiotherapy should be recommended based on the overall condition and preferences of the patient, including treatment goals and whether aggressive treatment is desired.

Chapter 7. Radioactive iodine therapy for differentiated thyroid cancer

Note 7-1. Definition, indications, and methods of radioactive iodine (RAI) therapy

As delineated in the 2015 ATA guidelines [230], the international consensus is to classify the administration of RAI to patients with differentiated thyroid cancer (DTC) into three categories: “RAI remnant ablation”, aimed at eradicating normal follicular cells in patients presumed to have no residual tumor; “RAI adjuvant therapy”, for patients who may have microscopic residual disease; and “RAI therapy”, for patients with visible residual tumors or distant metastases [111, 231, 232] (Table 14).

The primary objective of “ablation” is to optimize the utilization of serum Tg levels in postoperative DTC patients. The ESTIMABL1 trial [233] and the HiLo trial

[234] have demonstrated that the combination of rhTSH preparation and 1.1 GBq (30 mCi) of RAI offers equivalent efficacy to the thyroid hormone withdrawal (THW) method combined with 7.4 GBq (200 mCi) for low-risk patients. Conversely, for low-risk patients, the necessity of ablation has been questioned. Multiple studies have indicated a lack of significant difference in recurrence rates between groups with and without ablation following total thyroidectomy, as assessed by US of the neck, high-sensitivity serum Tg measurement (sensitivity, 0.1–0.2 ng/mL), and serum TgAb measurement [235–239]. RAI therapy thus does not seem necessary for low-risk DTC patients.

“Cancer treatment” refers to RAI therapy administered to patients with residual tumors identifiable through morphological diagnostics [111, 231]. Evaluating the efficacy of such treatment requires a comprehensive assessment that includes diagnostic imaging using scintigraphy, serum Tg levels, serum TgAb titers, and clinical symptomatology. Serum Tg offers a critical biomarker for estimating total tumor burden within the body, and the Tg doubling time correlates with prognosis. However, disease progression does not occur uniformly across all residual lesions; rapid and critical changes can emerge in a limited number of sites. Therefore, in addition to systemic evaluation using serum Tg, evaluating the changes in each lesion individually is crucial. Repeated administration of ineffective RAI therapies may exacerbate tumor-related symptoms or promote disease progression due to TSH stimulation during treatment [240]. Reassessing the treatment strategy at appropriate intervals rather than continuing RAI therapy indiscriminately is therefore imperative.

“Adjuvant therapy” refers to RAI therapy applied to patients in an intermediate state between ablation and treatment in terms of staging, to improve disease-free survival [111, 231]. This explicitly includes RAI therapy for patients suspected of harboring microscopic residual tumors. Given the vast array of cases in this category, differences in institutional perspectives are likely to influence patient selection, so detailed descriptions are omitted here. A dose of 3.7 GBq (100 mCi) or more is

Table 14 Classification of radioactive iodine (RAI) Therapy

Name	RAI remnant ablation	RAI adjuvant therapy	RAI therapy
Target and Intent	Elimination of thyroid remnant tissue for patients considered as having no residual tumor	Removal of cancer cells in patients with suspected microscopic residual tumors invisible on diagnostic imaging	Treatment for patients with macroscopic residual tumors or distant metastases
Purpose	Facilitation of follow-up	Prevention of recurrence, improvement of disease-free survival	Treatment of remaining cancer
I ¹³¹ dose	1.1–3.7 GBq (30–100 mCi)	3.7–5.6 GBq (100–150 mCi)	3.7–7.4 GBq (100–200 mCi)

recommended for adjuvant therapy [233, 241]. Due to the shortage of radioisotope therapy rooms in Japan, outpatient administration of 1.1 GBq (30 mCi) is often performed for these patients as “outpatient ablation”. However, acknowledging that this practice diverges from international standards is essential.

CQ 7-1.

Is rhTSH-aided RAI therapy recommended for DTC patients?

Recommendation statement

1. In DTC patients without distant metastases, rhTSH preparation for RAI adjuvant therapy is recommended.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 78%

2. In metastatic DTC patients, avoidance of rhTSH preparation for RAI therapy is recommended.

Certainty of evidence: D

Strength of recommendation: Strong; **Consensus rate:** 78%

Outcomes considered

- Recurrence rate in DTC patients without distant metastases
- Objective response rate (ORR), OS, and progression-free survival (PFS) in metastatic DTC patients
- Adverse events (AEs)
- Health-related quality of life (HRQOL)
- Ease of treatment preparation
- Medical costs

Evidence

- No prospective studies have compared recurrence rates of THW and rhTSH preparation for RAI therapy in intermediate- or high-risk DTC without distant metastases as defined by ATA guidelines.
- Three retrospective studies of intermediate- and high-risk DTC without distant metastases have demonstrated no significant difference in recurrence rates of RAI therapy with rhTSH and THW.
- Four retrospective studies targeting metastatic DTC patients showed no significant difference in PFS and OS between RAI therapy with rhTSH and THW. However, sample sizes in these studies were limited.
- Whether rhTSH stimulation reduces AEs is unclear. The stimulation from THW causes transient hypothyroidism and decreases in HRQOL.
- Although specific reports on the ease of preparation for treatment are lacking, RAI therapy with rhTSH appears to be more manageable.
- In terms of medical costs, rhTSH is more expensive than THW.

Summary and discussion of the literature

In 2009, rhTSH was approved in Japan for use in combination with diagnostic scintigraphy using radioiodine and serum Tg tests or as an adjunct to the Tg test alone in DTC patients who have undergone total or subtotal thyroidectomy. In 2012, rhTSH gained further authorization to assist in RAI ablation of residual thyroid tissue in DTC patients without distant metastases who had undergone these operations. As noted in Note 7-1, 1.1 GBq (30 mCi) of ^{131}I has recently been supported for remnant ablation. However, data supporting the additional approval for these indications were based on classical RAI ablation with administration of 3.7 GBq (100 mCi), aligning with the dosage for current RAI adjuvant therapy [242]. When RAI ablation is included as an objective, administration of 3.7 GBq (100 mCi) with rhTSH in DTC patients without distant metastases lies within the scope of insurance coverage in Japan. Based on this context, CQ 7-1 reviews the literature on THW and rhTSH, focusing on the rate of recurrence as the purpose of RAI adjuvant therapy in patients with intermediate- or high-risk DTC. While this CQ endorses rhTSH preparation for RAI adjuvant therapy, rhTSH preparation is still considered an alternative to stimulation by THW. The THW preparation for RAI adjuvant therapy is recommended across any risk classification. In addition, the rhTSH preparation for RAI therapy in patients with distant metastatic DTC constitutes an off-label use and thus warrants careful consideration.

1) Recurrence rate in DTC patients without distant metastases

Dehbi *et al.* [243] conducted a randomized controlled trial (RCT) (HiLo trial) across 29 facilities in the United Kingdom, focusing on patients with low- or intermediate-risk DTC, including 147 intermediate-risk cases out of a total of 434. The trial compared recurrence rates of THW and rhTSH preparation for RAI therapy. Seven-year recurrence rates were 5.0% (95%CI 2.5–10.0%) for the THW preparation and 8.3% (95%CI 4.5–15.3%) for the rhTSH preparation, with no significant difference observed between groups. Nevertheless, these findings require cautious interpretation as the trial also included low-risk cases and a low-dose 1.1 GBq (30 mCi) RAI therapy group.

Jeong *et al.* [244] retrospectively studied recurrence rates in T4 or N1b cases (total, 253 cases), comparing groups of rhTSH + 3.7 GBq (100 mCi) and THW + 5.6 GBq (150 mCi). Over an average follow-up of 43.6 ± 19.4 months, recurrence rates were 10.4% (13 of 125 cases) for the THW + 5.6 GBq (150 mCi) group and 7.0% (9 of 128 cases) for the rhTSH + 3.7 GBq (100 mCi) group, with no significant difference ($p = 0.936$). Rosario *et al.* [245] examined short- and

long-term recurrence rates following RAI therapy in cN1b cases within the intermediate-risk group. Over an average observation period of 66 months, no significant differences in recurrence rates were seen between the rhTSH group (4 of 91 cases, 4.4%) and THW group (4 of 87 cases, 4.6%). Hugo *et al.* [246] reported on recurrence rates following RAI therapy in 586 cases, primarily comprising intermediate- and high-risk patients (321 cases treated with THW, 265 cases treated with rhTSH). Over a median follow-up of 9 years, recurrence rates were 1.5% for the rhTSH method and 1.2% for the THW method, showing no significant difference.

2) Treatment outcomes in cases with distant metastases

Some retrospective studies on cases with distant metastases have demonstrated no significant differences in progression-free survival (PFS) or OS between rhTSH and THW preparation [247-250]. However, sample sizes in those studies were minimal, rendering the outcome data insufficient. As previously mentioned, the use of rhTSH preparation for RAI therapy in patients with distant metastatic DTC is off-label in Japan. Consequently, at the time of writing, rhTSH preparation for RAI therapy in DTC patients with distant metastases cannot be recommended.

3) AEs, HRQOL and medical costs

The HRQOL is primarily impacted by hypothyroidism with these preparations and is not correlated strongly with the recurrence rate. In addition, AEs, HRQOL, and related medical costs incurred from high-dose 3.7 GBq (100 mCi) RAI therapy in low-risk DTC patients share many similarities with those observed in intermediate- and high-risk cases. The literature was therefore reviewed without regard to risk classification.

Mallick *et al.* [234] reported on AEs, HRQOL, and medical costs associated with rhTSH and THW methods for RAI therapy in the Hilo trial, which was conducted at 29 UK facilities. Incidences of AEs were similar between the rhTSH and THW groups at 1 week (23% vs. 30%, $p = 0.11$) and at 3 months after treatment (27% vs. 24%, $p = 0.34$), with no severe AEs causally related to RAI treatment. In addition, the average cost for high-dose RAI therapy was £1,582 (\$2,515) in the rhTSH group and £1,056 (\$1,679) in the THW group. During the 4 weeks preceding RAI treatment, symptoms related to hypothyroidism were less frequent in the rhTSH group (with most comparisons yielding $p < 0.001$). In a patient survey that included questions about working status, 44.6% of the rhTSH group continued working before RAI treatment, compared to 28.7% of the THW group ($p < 0.001$). The median number of days absent from work was reported as 1 day in the rhTSH group and 5 days in the THW group ($p = 0.17$).

Borget *et al.* [251] reported on HRQOL and the

cost-effectiveness of RAI treatments, using two doses (1.1 GBq or 3.7 GBq) and two preparations (rhTSH or THW methods), in an RCT of low-risk DTC patients (the ESTIMABL study). The rhTSH group avoided the transient deterioration of HRQOL caused by THW methods while demonstrating higher quality-adjusted life years (QALYs) than the THW group (an increase of 0.013 QALYs/person). In France, the probability that rhTSH would be cost-effective under a €50,000/QALY threshold was 47%, suggesting that at current prices, rhTSH may not be cost-effective.

Further, the ATA guidelines recommend consideration of rhTSH for any DTC patients with comorbidities not amenable to THW before RAI therapy. Significant comorbidities include medical or psychiatric conditions that may lead to severe AEs as a result of hypothyroidism, or an inability to obtain adequate endogenous TSH response from THW [230].

CQ 7-2.

Is administration of 1.1 GBq (30 mCi) recommended for RAI adjuvant therapy?

Recommendation statement

RAI adjuvant therapy with 1.1 GBq (30 mCi) is not recommended.

Certainty of evidence: D

Strength of recommendation: Weak; **Consensus rate:** 89%

Outcomes considered

- Rate of successful ablation
- Recurrence rate
- Disease-specific survival rate
- AEs

Evidence

- No prospective studies have compared the recurrence rate and disease-specific survival between low- and high-dose RAI therapy groups for intermediate- and high-risk DTC.
- A meta-analysis targeting studies of intermediate- and high-risk DTC estimated that successful ablation with initial RAI therapy influences the recurrence rate.
- Several studies including cases with intermediate risk DTC have reported no significant difference in rates of successful ablation between low-dose RAI therapy and higher doses.
- The incidence of AEs was higher in high-dose groups than in low-dose groups.

Summary and discussion of the literature

No prospective studies have investigated recurrence rates and OS with different I¹³¹ doses specifically targeting patients with intermediate- and high-risk DTC. The literature on recurrence rates is limited to a single retrospective study. Thus, CQ 7-2 also inspected the

successful ablation rate, which may potentially influence recurrence rates. Successful ablation is generally defined as resulting in low serum Tg levels and no structural disease on diagnostic imaging after RAI therapy. However, interpretations of successful ablation have varied across studies, and the definitions provided in the literature are annotated in parentheses. In this context, a low dose refers to 1.1 GBq (30 mCi), while a high dose refers to 3.7 GBq (100 mCi) or higher.

Klain *et al.* [252] conducted a meta-analysis of 3,103 patients with intermediate- or high-risk DTC treated using RAI therapy. They reported that the successful ablation rate (defined as the absence of abnormalities on US of the neck and low Tg levels on TSH stimulation) was significantly higher in the intermediate-risk group (72%) compared to the high-risk group (52%). Further, among the intermediate-risk cohort with an average follow-up of 6.4 ± 1.4 years, the recurrence rate was 2% in patients who achieved successful ablation with the initial RAI treatment, compared to 14% in those who did not attain successful ablation at initial RAI therapy. Successful ablation with first-time RAI therapy is thus suggested to markedly influence recurrence rates.

In a retrospective study with a small sample size, Watanabe *et al.* [241] investigated recurrence rates for groups with low- ($n = 17$) and high-dose RAI ($n = 31$) among postoperative DTC patients with microscopically positive margins. Recurrence rates within median observation periods of 36.2 months for the low-dose group and 43.8 months for the high-dose group were reported as 52.9% (9 cases) and 22.5% (7 cases), respectively.

Few reports have described successful ablation rates for different doses in initial RAI therapy targeting only intermediate- and high-risk DTC patients. Abe *et al.* [253] retrospectively reported a successful ablation rate of 23.4% (negative on diagnostic scintigraphy, Tg < 2 ng/mL on TSH stimulation) in 119 patients with intermediate- and high-risk DTC treated using low-dose RAI therapy. The successful ablation rate was notably lower compared to that described in the meta-analysis by Klain *et al.* [252].

In another retrospective study, Han *et al.* reported no significant difference in successful ablation rates between low- and high-dose groups among cases of intermediate-risk DTC characterized by microscopic extrathyroidal extension, primary tumor size ≤ 2 cm and absence of cervical lymph node metastasis [254]. Successful ablation was assessed based on negative findings for serum Tg and TgAb-negative results on TSH stimulation, with no abnormal lymph nodes detected on neck US. However, as this study focused only on a subset of intermediate-risk patients, extrapolating these findings to the entire intermediate- and high-risk cohort is inappropriate.

Given such findings, it remains unclear whether low-dose RAI adjuvant therapy for intermediate- and high-risk DTC patients decreases the successful ablation rate and subsequently increases the recurrence rate. We cannot rule out the possibility that insufficient dosages might increase recurrence rates. A universal recommendation of low-dose RAI as adjuvant therapy is thus challenging. However, in Japan, high-dose RAI therapy can only be performed in radioisotope therapy rooms, raising concerns about missing the optimal timing for RAI adjuvant therapy due to extended wait times. The Japanese Society of Nuclear Medicine is actively working towards approving 3.7 GBq (100 mCi) on an outpatient basis, but this change may take time. Until such approval is granted, performing RAI adjuvant therapy with 1.1 GBq (30 mCi) may be unavoidable with a complete understanding of the issues above.

Regarding AEs, an RCT by Qu *et al.* [255] demonstrated that the rate of AEs following RAI therapy for low- and intermediate-risk DTC was 18% in the low-dose group and 39% in the high-dose group. In addition, Cheng *et al.* [256] reported in a meta-analysis of DTC (not stratified by risk classification) that the incidence of early post-treatment AEs was lower in the low-dose group than in the high-dose group. Based on these findings, high-dose RAI therapy is suggested to be associated with an increased incidence of early post-treatment AEs compared to low-dose RAI therapy.

Column 7-1. AEs and their management

RAI therapy can induce side effects, including sialadenitis and dacryoadenitis, glandular dysfunction related to these inflammations, gastrointestinal disturbances such as nausea and vomiting, bone marrow suppression, and gonadal dysfunction. The incidence of secondary malignancies following RAI therapy remains unknown.

Sialadenitis [257] and gastrointestinal disturbances such as nausea and vomiting [258] are relatively common as early side effects of RAI therapy. Swelling and pain in the salivary glands and nausea and vomiting occur in a few to several dozen percent of cases. Various formulations, such as including vitamin E or vitamin C, or as a candy, have been tried to reduce damage to the salivary glands, but none have proven consistently effective [259]. We can manage symptoms using analgesics and antiemetics in the acute phase. As the cumulative dose increases, however, declines in salivary gland secretions may become more pronounced. Dacryoadenitis is less frequently encountered but can occasionally result in persistent symptoms, such as reduced tear production [260]. Taste disturbances resulting from damage to the taste buds on the tongue may also occur, but typically

recover over time [261].

Therapeutic doses of RAI can also cause bone marrow suppression, but intervention is rarely needed [258, 261]. Bone marrow suppression is enhanced with increasing cumulative doses.

Transient reductions in ovarian and testicular function can occur following RAI therapy [262]. Sperm cryopreservation is recommended for males expecting to receive doses exceeding 14 GBq (approximately 380 mCi) [263]. Women should avoid pregnancy for 1 year after RAI therapy [264]. On the other hand, long-term infertility, miscarriage, and fetal malformation rates do not appear to be increased by RAI [265].

The risk of secondary malignancies following RAI therapy remains a topic of debate. An analysis of 27,050 cases from the US Surveillance Epidemiology and End Results (SEER) database suggested an increase in hematological malignancies, including leukemia, and solid tumors, including breast cancer, after RAI therapy [266]. Another SEER-based study indicated an increased incidence of breast cancer among the RAI-treated thyroid cancer cohort compared to both non-RAI-treated thyroid cancer patients and the general population [267]. However, a large-scale study involving 200,247 cases found no increase in the incidence of breast cancer due to RAI

therapy [268]. Similarly, a study of 24,318 cases from multiple institutions did not demonstrate any increase in the risk of secondary cancers attributable to RAI therapy [269].

Chapter 8. Treatment of advanced differentiated thyroid carcinoma

Clinical algorithm 8-1. Management of differentiated thyroid carcinoma (DTC) with unilateral recurrent laryngeal nerve palsy (Fig. 9)

CQ 8-1.

Is shave excision recommended for cases with recurrent laryngeal nerve (RLN) invasion and without preoperative vocal cord palsy?

Recommendation statement

Shave excision without residual cancer is recommended for cases with RLN invasion and without preoperative vocal cord palsy.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 89% (re-vote)

Outcomes considered

- Prognosis (local recurrence)

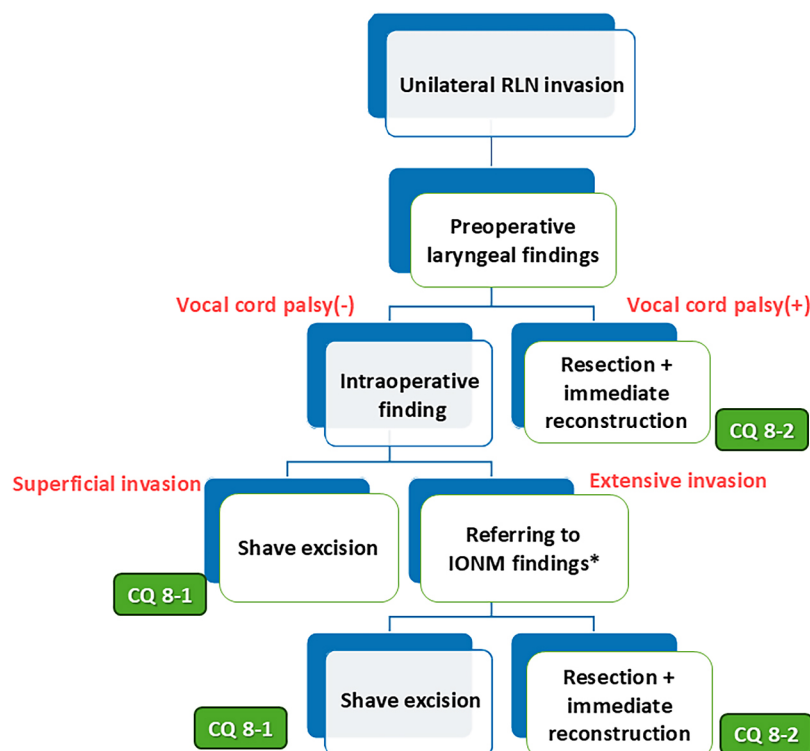


Fig. 9 Clinical algorithm 8-1. Management of differentiated thyroid carcinoma (DTC) with unilateral recurrent laryngeal nerve (RLN) palsy

*Refer to electromyographic potentials from stimulation of the RLN at the proximal end of the infiltrate by IONM
IONM: intraoperative neuromonitoring.

- Phonatory function
- Health condition from the patient's perspective

Evidence

- The rate of tumor recurrence at the shaved site was estimated as 5% in patients with extra-thyroidal extension of PTC limited to the RLN.
- Shave excision might be followed by permanent vocal cord paralysis with a probability of 8–25% in patients without preoperative RLN palsy.
- No reports have inquired about patient perspectives related to surgery in cases of RLN infiltration.

Summary and discussion of the literature

All the literature pertinent to this CQ involved retrospective studies. In cases of RLN involvement with preoperative vocal cord palsy, the degree of infiltration is often so severe that combined RLN resection is recommended [270]. On the other hand, even if vocal cord palsy is not present preoperatively, intraoperative findings of RLN involvement are not uncommon [271]. In cases of RLN involvement without vocal cord palsy, nerve infiltrations are often superficial to partial. For cases with superficial (to the epineurium) invasion of RLN, shave excision is recommended to preserve the RLN with sharp dissection to avoid residual tumors and preserve vocal cord function [272]. Electromyographic potentials from RLN stimulation at the proximal end of the infiltrate can help determine whether the RLN should be resected [273]. Tumor recurrence at the shaved site was estimated to occur in 5% of patients showing extra-thyroidal extension of PTC limited to the RLN. Shave excision might be accompanied by permanent vocal cord paralysis in 8–25% of patients without preoperative RLN palsy. Recovery of vocal cord mobility is often seen within 6 months [274–279]. Shave excision for advanced infiltration beyond the epineurium and into the perineurium, even in the absence of preoperative vocal cord palsy, almost always results in microscopic residuals. Performance status and swallowing function should therefore be considered when deciding whether to perform shave excision or resection of the RLN. Particularly in elderly patients with swallowing dysfunction, the risk of aspiration is increased due to RLN palsy, which may cause aspiration pneumonia. No reports have clarified patient perspectives related to surgery in cases of RLN involvement.

CQ 8-2.

Is RLN reconstruction recommended for cases undergoing nerve resection?

Recommendation statement

RLN reconstruction at the time of nerve resection is recommended for cases undergoing nerve resection.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 67%

Outcomes considered

- Postoperative phonatory function
- Health condition from the patient's perspective

Evidence

- Phonatory function recovers within 1 year after nerve reconstruction.
- No reports have clarified patient perspectives related to RLN reconstruction surgery.

Summary and discussion of the literature

RLN invasion from DTC has little impact on prognosis or recurrence [278, 280–282], but significantly affects functional prognosis, as unilateral vocal cord palsy results in hoarseness and dysphagia, while bilateral vocal cord palsy causes airway constriction. RLN resection for unilateral RLN infiltration fixes the affected vocal folds in a paramedian position. Atrophy of the intralaryngeal muscles then leads to enlargement of the glottic gap, contributing to further progression of hoarseness and dysphagia. RLN reconstruction does not restore vocal cord movement due to the misdirected regeneration of the nerve, but often improves phonatory function by fixing the vocal cords in the median position and preventing atrophy of the intralaryngeal muscles, although several months is required. RLN reconstruction at the same time as nerve resection is therefore recommended for cases undergoing nerve resection.

All literature on RLN reconstruction involves retrospective studies. With immediate reconstruction of the RLN, recovery of phonatory function is expected within 1 year [283–285]. Although recovery of phonatory function takes longer with RLN reconstruction than with two-stage phonatory reconstructions such as type I thyroplasty or arytenoid internalization, improvements in speech function are expected to be equal or better [286, 287].

Some surgical techniques in RLN reconstruction include end-to-end anastomosis, free nerve grafting, anastomosis of the RLN to the ansa cervicalis, and anastomosis of the RLN to the vagal nerve [283]. All reconstruction methods are expected to improve phonatory function and should be selected based on intraoperative findings. In cases with RLN involvement at the ligament of Berry, identifying the peripheral side of the nerve after resection is difficult. The laryngeal approach, in which the inferior pharyngeal constrictor muscle is divided along the lateral edge of the thyroid cartilage and the nerve is identified under the muscle or behind the thyroid cartilage, is helpful for RLN reconstruction in cases of RLN involvement at the ligament of Berry [288, 289].

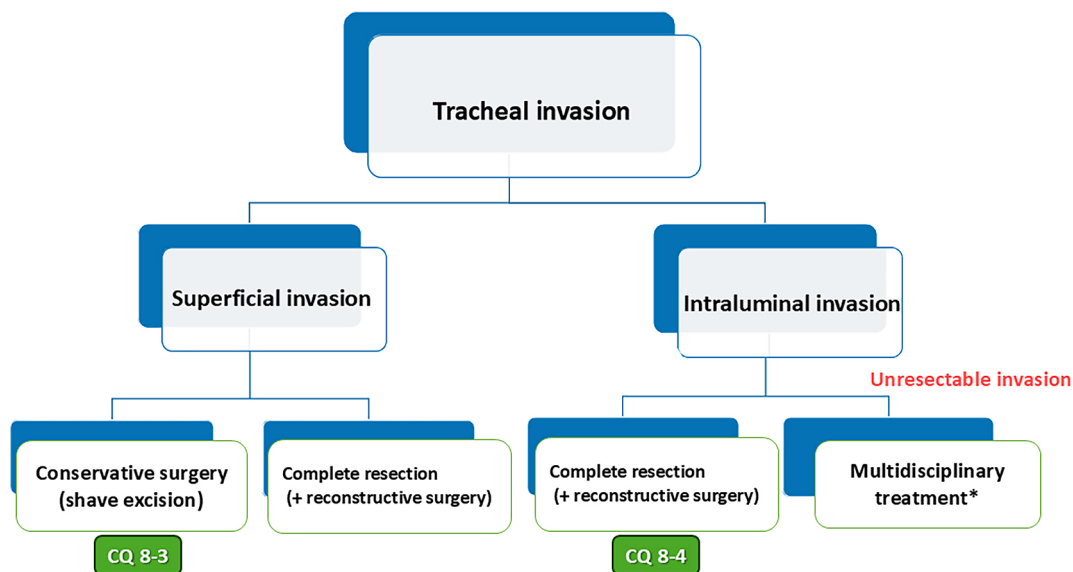


Fig. 10 Clinical algorithm 8-2. Management of DTC with tracheal invasion

* Multidisciplinary treatment: external radiation therapy, cancer chemotherapy, tracheal stenting.

Clinical algorithm 8-2. Management of DTC with tracheal invasion (Fig. 10)

CQ 8-3.

Is shave excision recommended for cases with superficial invasion of the trachea?

Recommendation statement

Shave excision without gross residuals is recommended for cases with superficial tracheal invasion.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 67% (re-vote)

Outcomes considered

- Prognosis (carcinoma death)
- Local recurrence
- Health condition from the patient's perspective

Evidence

- Prognosis was poor in cases of non-resection or incomplete resection (gross residuals) of tracheal invasion.
- The recurrence rate after shaving excision (tracheal wall) was about 5%.
- No reports have clarified patient perspectives related to surgery in cases of superficial tracheal invasion.

Summary and discussion of the literature

Surgical resection plays a significant role because airway invasion by DTC causes airway narrowing and dysphagia. At the same time, the airway is a vital organ for breathing, speech, and swallowing, and tracheal resection may thus reduce postoperative QOL. The decision to conduct tracheal resection must balance reductions in

QOL due to resection and the expected postoperative prognosis.

Thyroid cancer invades the airways from the outer membrane and moves toward the lumen. Deep invasion extending into the lumen requires combined airway resection (see CQ 8-4). In cases of superficial tracheal invasion, one surgical option is shave excision, involving sharp excision of only the superficial tracheal invasion and preservation of the tracheal tubular structure. Combined airway resection for superficial invasion of the trachea is curative, but requires primary reconstruction or tracheal stoma formation and staged closure. Meanwhile, shave excision does not require tracheal reconstruction or closure of a tracheocutaneous fistula, but increases the risk of recurrence due to residual tumor at the resection margin. In particular, shave excision for invasion beyond the tracheal cartilage, across multiple tracheal cartilages, or involving the membranous portion of the trachea is associated with a high risk of tumor remnants at the resection margins [290].

All reports on combined airway resection in cases of tracheal invasion have been retrospective studies from single centers with limited numbers of cases. Although bias is present in that the degree of invasion is generally more substantial in cases of no or incomplete resection with gross residual than in cases of complete resection, a comparison of complete resection groups with no or incomplete resection groups showed worse prognosis for the latter [291-294].

No reports have directly compared outcomes for tracheal resection and shave excision for superficial

invasion. Most reports recommended shave excision for superficial tracheal invasion based on outcomes of achieving a reasonable local control rate (71.9–95%) [295–298] and good prognosis [295, 296, 299, 300]. Many of those reports also showed microscopic residuals at the resection site [295, 297, 301]. Ito *et al.* reported that about half of the patients who underwent shave excision for superficial tracheal invasion by PTC and for whom intraoperative findings confirmed macroscopic curative resection showed microscopic residuals at the cut surface. However, the local control rate for these patients was high, leading to the conclusion that microscopic residuals had little impact on local recurrence [295]. On the other hand, some reports recommended tracheal resection over shave excision [302, 303]. Tsai *et al.* reported on shave excision performed in 16 cases of superficial tracheal invasion, with additional adjuvant therapy in 15 of these cases. Local recurrence was observed in 8 cases, and three patients died due to airway recurrence [303]. Although the details of local recurrence and tumor residuals were not described, gross residuals were seen in seven cases, suggesting an association between gross residuals and poor local control.

No reports have described patient perspectives related to surgery in cases of superficial tracheal invasion.

In summary, shave excision for superficial tracheal invasion may represent a valid treatment option, since local control was excellent in many cases where macroscopic curative resection was achieved, even with microscopic residuals. However, local control was poor in cases of gross residuals. It is essential to evaluate the extent of tracheal invasion, including degree of progression, and to consider the skills of the treatment team when selecting a surgical approach.

CQ 8-4.

Is complete resection of the tracheal wall (and reconstruction of the trachea) recommended for cases with intraluminal invasion of the trachea?

Recommendation statement

Complete resection of the invaded tracheal wall (and reconstruction of the trachea) is recommended for cases of intraluminal invasion of the trachea.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 67%

Outcomes considered

- Prognosis (local recurrence, carcinoma death)
- Surgical complications
- Postoperative functions (rate of trachea stomal closure)
- Health condition from the patient's perspective

Evidence

- Five- and 10-year disease-specific survival rates after

sleeve resection of the trachea were 75.8–90% and 54.5–69.2%, respectively. Conversely, 5- and 10-year disease-specific survival rates after window resection of the trachea were 78.9–94% and 60.8–92%, respectively.

- The recurrence rate of tracheal invasive sites after sleeve resection and window resection was 0–12.3% and 4–17.1%, respectively.
- The incidence of postoperative complication rates for sleeve resection ranged from 14.1% to 27%, with perioperative mortality in 2.0% of patients. The incidence of postoperative complications after window resection was 19.8%.
- Permanent tracheal stoma remained in 4% of patients after sleeve resection and 16.5–61% after window resection.
- No reports have clarified patient perspectives related to surgery in cases of intraluminal tracheal invasion.

Summary and discussion of the literature

Tracheal resection is required when DTC invasion reaches the tracheal lumen (tracheal mucosa). The surgical procedure for such lesions is sleeve or partial resection (wedge resection and window resection). Sleeve resection is a technique in which the trachea in the infiltrated area is resected in a tubular form and closed by end-to-end anastomosis in one stage. Partial tracheal resection is where the trachea is resected in the infiltrated area with a safety zone, often creating a tracheal stoma in the tracheal defect. Closure of the tracheal stoma is achieved in two stages. Tracheal invasion that reaches the submucosa spreads more circumferentially than longitudinally [304, 305]. Because partial tracheal resection increases the likelihood of residual tumor at the resected end and increases the number of cases in which tracheal stomal closure proves difficult, many reports have recommended sleeve resection and concurrent end-to-end anastomosis.

All reports on tracheal resection of intraluminal tracheal invasion have been retrospective studies. A systematic review of sleeve resection showed that 5- and 10-year disease-specific survival rates after sleeve resection were 75.8–90% and 54.5–69.2%, respectively [306]. The postoperative complication rate was reported as 27% (95%CI 20.0–36.0%) and the perioperative mortality rate as 2.0% (95%CI 1.0–4.0%). Permanent tracheal stoma remained in 4% of patients (95%CI 2.0–8.0%) after sleeve resection. In contrast, a systematic review of both surgical techniques found that postoperative complications after sleeve and window resections were 14.1% (95%CI 8.3–19.9%) and 19.8% (95%CI 6.9–32.8%), respectively [307]. Anastomotic failure after sleeve resection was observed in 2.2% of patients (95%CI 1.2–3.1%), and the limit of end-to-end anastomosis was

reported as seven rings (5–6 cm), with 2–3 rings being resected most often. According to reports with more than 40 window resections, pathological residuals at the resection margins were found in 35% by Ito *et al.* and 65.8% by Ebihara *et al.* [308, 309]. Still, no difference in local recurrence rates was seen between cases with positive and negative margins in either report. Recurrence rates at tracheal invasive sites after window resection were reported as 4–17.1%, with disease-specific survival rates of 78.9–94% at 5 years and 60.8–92% at 10 years [308–310]. Conversely, recurrence rates at tracheal invasive sites after sleeve resection ranged from 0% to 12.3% [303, 304, 311, 312].

After window resection, 16.5–61% of patients required a permanent tracheal stoma. Moritani *et al.* reported that window resection in 76 cases left a permanent tracheal stoma in 61% of cases and that cases with resection of more than half of the tracheal circumference were more likely to require tracheal stoma [310]. Ebihara *et al.* reported that although closure of the tracheal stoma is performed in stages, this method is effective in elderly patients because of the reduced risk of complications and the avoidance of a need for cervical fixation [309].

No reports have clarified patient perspectives related to surgery in cases of intraluminal tracheal invasion.

In summary, sleeve resection and concurrent end-to-end anastomosis for intraluminal trachea invasion are based on the fact that residual tumor is absent from the resection margin, prognosis is better, fatal postoperative complications occur less frequently, and better functional reconstruction is achieved. On the other hand, window resection is reported less commonly but offers better prognosis, does not require cervical fixation, and is more beneficial for elderly patients. Evaluating the extent of tracheal invasion (including the degree of progression) is essential, and the skills of the treatment team must be considered when selecting a surgical approach. Selecting a surgical approach also requires evaluation of the specific situation of the patient (tumor stage, performance status, and wishes of the patient and their family) and the skills of the medical team.

Column 8-1. Surgical treatment of laryngeal invasion, esophageal/pharyngeal invasion, great vessel invasion, and parapharyngeal and mediastinal lymph node metastasis of DTC

When considering the surgical resection of tumors involving the larynx, esophagus/pharynx, great vessels, or parapharyngeal or mediastinal lymph node metastases, surgical indications should be determined in close collaboration with a specialized team that includes experienced head and neck surgeons, respiratory surgeons, and vascular surgeons.

Many patients with locally advanced DTC that is considered unresectable develop airway obstruction and bleeding, which represent potential causes of death [313]. Surgical resection is thus recommended for local control. Like tracheal invasion, many reports support functional preservation surgery with shave excision for laryngeal, esophageal/pharyngeal, and vascular invasion if the invasion is superficial, and combined resection and reconstruction for deep invasion of these organs [314, 315]. Shave excision for superficial invasion is acceptable as microscopic residuals do not affect prognosis or recurrence. Invasion into these organs occurs not only from direct invasion from primary tumors, but also from metastatic lymph nodes. Invasion involving multiple organs is not uncommon and may necessitate extensive surgery [316].

The first choice of treatment for locally advanced tumors is surgical resection. The surgical indication should be determined in consultation with a specialized team based on a comprehensive assessment of tumor extent, surgical complications, expected postoperative declines in QOL (including swallowing and speech functions), and predicted prognosis.

1) Laryngeal invasion

Laryngeal invasion by thyroid carcinoma occurs directly through the thyroid and cricoid cartilages into the paraglottic space by an anterior route or into the paraglottic space by extension around the posterior border of the thyroid cartilage. The pharynx can also be invaded by posterior extension of thyroid carcinoma around the thyroid cartilage and into the pyriform sinus [317]. For resection of tracheal invasion involving the cricoid cartilage, predicting postoperative functional outcomes is relatively easy based on the extent of airway resection and RLN involvement. On the other hand, when the invasion involves the thyroid cartilage or intralaryngeal space, predicting postoperative functional outcomes becomes difficult. A laryngeal framework resection, including shave excision, is often performed for superficial thyroid cartilage invasion. Laryngeal function is preserved if the resection can be limited to the unilateral thyroid cartilage lamina. Involvement of the paraglottic or intralaryngeal space is infrequent, but requires intralaryngeal resection according to the degree of invasion. Partial laryngectomy or vertical hemi-laryngectomy can be used [318, 319].

Preservation of laryngeal function becomes difficult in cases of extensive invasion, and total laryngectomy becomes increasingly valid as a treatment option [320]. However, since laryngeal invasion by DTC is often confined to one side of the larynx and resection can be expected to affect long-term prognosis, total laryngectomy should not be chosen without careful consideration.

2) Esophageal/pharyngeal invasion

The esophageal/pharyngeal musculature may become involved through direct tumor extension or extracapsular extension of the involved paratracheal lymph nodes. The esophageal mucosa represents a tough barrier to penetration and is rarely involved on the luminal surface. Most cases can be treated with muscle layer resection [316]. The esophageal muscular layer consists of the internal circular and lateral longitudinal muscles. If the lateral muscle layer is resected, oral intake can be resumed in the early postoperative period. Even if resection of the muscular layer partially exposes the mucosal layer, esophageal reconstruction remains unnecessary if the tubular structure can be preserved. In cases of total cervical esophagectomy with laryngectomy, autografts of luminal organs such as free jejunum are often used, while partial esophagectomy is often reconstructed using thin skin flaps, such as free forearm flap.

3) Great vessel invasion

The carotid artery is elastic, with a three-layered structure comprising the intima, tunica media, and adventitia. With resection of the adventitia alone, the risk of arterial rupture or aneurysm formation is low, but arterial reconstruction is required if resection extends to the tunica media. Because the diagnosis of great vessel invasion is challenging on preoperative imaging, surgery for suspected carotid artery invasion also requires preparation for arterial reconstruction. Although carotid reconstruction reduces rates of complications (15–20%) and mortality (16–20%), the frequency of postoperative complications in cases of carotid artery invasion by head and neck squamous cell carcinoma (HNSCC) remains high [321, 322]. Circumferential involvement of more than 180° on contrast-enhanced CT or 270° on contrast-enhanced MRI has been reported as a predictor of great vessel invasion [323, 324].

Many studies concerning the surgical treatment of carotid artery invasion have been reported for HNSCC, compared to few reports regarding great vessel invasion by DTC. Moritani *et al.* reported outcomes for 49 patients with carotid artery invasion by PTC, 47 of whom underwent subadventitial resection and two of whom underwent carotid artery resection and reconstruction. All 20 primary cases underwent subadventitial resection, resulting in complete resection, with a 10-year disease-specific survival rate of 69.3%. Local or regional recurrence was observed in 14 patients (29%), but the recurrence rate in the area of carotid artery invasion was 2%. Treatment outcomes for carotid artery invasion by PTC compared favorably with those for HNSCC, possibly due to the lower biological grade of PTC [325]. The great vessels after subadventitial resection are highly vulnerable to external forces or infection. Locally

advanced DTC with carotid artery invasion often involves multiple organs. Particular attention should therefore be paid to infection control in cases with intraluminal resection of the aerodigestive tract.

4) Lymph node metastasis in the parapharyngeal space (PPS)

The PPS is well described as an inverted pyramid shape, with the base at the skull base and the apex at the greater cornu of the hyoid bone. The posterior portion of the PPS is surrounded by internal carotid arteries, internal jugular veins, lower cranial nerves (cranial nerves IX–XII), and sympathetic nerves. Metastatic tumors tend to occur in this posterior portion. Due to the anatomical shape of the PPS, which is difficult to approach surgically due to the barrier presented by the mandible and the fact that tumors do not become symptomatic until fairly large, parapharyngeal metastases are sometimes considered unresectable when detected. Even if resectable, functional impairment is likely due to lower cranial nerve deficits [326].

Most parapharyngeal metastases of thyroid cancer are recurrent. However, metastases to the PPS can occur on rare occasions, even in primary cases, because lymph flows directly from the superior pole of the thyroid gland to the PPS in about 20% of cases [327]. In recurrent cases, neck dissection and/or metastases in cervical lymph nodes might alter the direction of lymphatic drainage, resulting in unusual metastases to lymph nodes in the PPS [328]. Approaches for PPS surgery reportedly include transoral, transcervical, and transcervical-transparotid approaches, with or without several mandibulotomies. Many reports have described removal of metastases using the transcervical approach. Regardless of the approach, defining the locations of the major organs and parapharyngeal metastases in the PPS and securing the operative field are important. The lower cranial nerves are also susceptible to damage from tumor invasion and the excision itself. The risks of postoperative upper airway obstruction or dysphagia due to pharyngeal swelling should also be kept in mind [329].

5) Lymph node metastasis in the mediastinum

The peri-thyroid glandular lymph network has two main drainage pathways. The primary lymph drainage system comprises the lymph vessels in the central compartment, which stretch down along the pre- and paratrachea to the upper mediastinal nodes. The secondary lymph drainage system comprises lateral lymph vessels along the jugular vein. Direct lymphatic communications with the lateral cervical nodes are also present, providing lymphatic communications to the upper mediastinal nodes *via* central compartment nodes. Given these lymphatic flows, the upper mediastinum is a common site of thyroid cancer metastasis [330]. In particular,

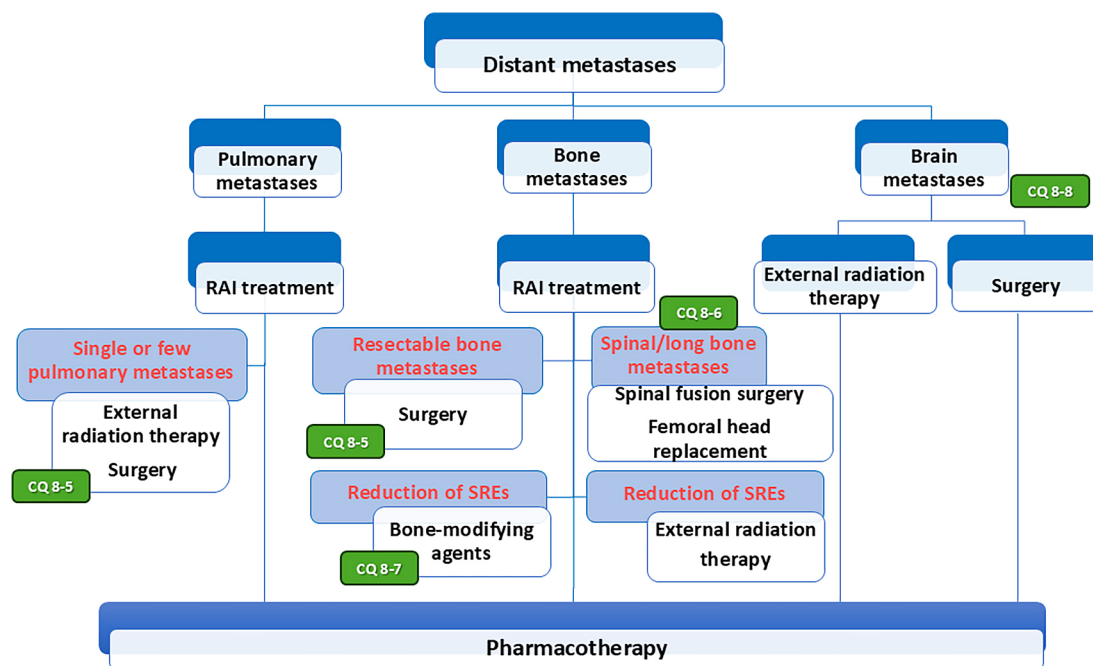


Fig. 11 Clinical algorithm 8-3. Treatment strategies based on sites of distant metastasis

RAI: radioactive iodine; SREs: skeletal-related events.

upper paratracheal metastases in the mediastinum along the RLN are common. Lymph node metastases in the pre-tracheal, para-esophageal, and lateral cervical regions, including the contralateral neck, are considered risk factors for mediastinal metastases [331].

Most reports on upper mediastinal dissection (UMD) for DTC have been concerned with UMD outcomes *via* the transcervical approach following central neck dissection. Few reports have described UMD using sternotomy. UMD *via* a transcervical approach is performed as an extension of central dissection, which is noninvasive and safe. This method should be considered in patients at risk of upper mediastinal metastases that can be removed *via* the transcervical approach [332]. On the other hand, mediastinal dissection by sternotomy is not recommended unless mediastinal metastases are suspected from preoperative imaging [333]. Two methods are used for the mediastinal approach: partial sternoclavicular joint and manubrium resection and sternotomy including L, inverted-L, inverted-T, and longitudinal incisions. Securing the surgical field and performing careful surgical manipulation is essential with either approach. Moritani *et al.* reported a 10-year survival rate of 60% after UMD for 58 cases of PTC. They concluded that UMD for patients with upper mediastinal metastases that are difficult to resect under a transcervical approach represents an effective method for improving patient prognosis [334]. Although the surgical indications should be determined based on tumor extent, operative stress, and

the specific situation of the patient, UMD for patients with upper mediastinal metastases may be a useful treatment option, as many cases can be expected to have a long-term prognosis.

Clinical algorithm 8-3. Treatment strategies based on sites of distant metastasis (Fig. 11)

CQ 8-5.

Is local therapy (surgery or radiotherapy) recommended for cases with a single metastasis or only a few bone or pulmonary metastases?

Recommendation statement

Local therapy for a single metastasis or only a few bone or pulmonary metastases is suggested when a contribution to the maintenance and improvement of QOL is expected.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 100% (re-vote)

Outcomes considered

- Prognosis (death due to carcinoma)
- Health condition from the patient's perspective

Evidence

- Surgical therapy is expected to improve prognosis and QOL when bone metastases are solitary or few and resectable.
- Bone metastasis pain without pathological fracture or spinal cord compression symptoms can be alleviated or

eliminated using external radiotherapy.

- Minimally invasive surgery is preferred for pulmonary metastases, and the number of resections should be limited to three or fewer.
- Stereotactic radiotherapy for pulmonary metastases can be expected to reduce or maintain tumor size in patients with few metastases that are considered high risk in terms of resection.
- No reports have clarified patient perspectives regarding local therapy for a single metastasis or only a few bone or pulmonary metastases.

Summary and discussion of the literature

The most common site of distant metastases (DM) of DTC is the lung (49%), followed by bone (25%), with simultaneous lung and bone metastases (BMs) occurring in approximately 15% of cases. BMs tend to occur in areas with abundant blood flow, followed by the spine (34.6%), pelvis (25.5%), sternum and ribs (18.3%), and limb bones (15.6%). BMs of DTC show an osteolytic pattern, and 50% of all such metastases are solitary [335, 336]. DM is more common with FTCs (7–28%) and PTCs (1.4–7%) [335, 337]. The first-line treatment for DM is RAI if emergency treatment is not required. For RAI-refractory cases, molecularly targeted therapy can be initiated according to the degree of tumor progression.

The treatment of DM aims to maintain and improve QOL and prolong survival. RAI therapy or molecularly targeted therapy for DM is expected to be effective as systemic therapy. In contrast, local therapy with surgery or radiotherapy can contribute to maintaining and improving QOL. For single or few BMs other than in the spine and long bones (see CQ9-6), surgical treatment may improve prognosis and QOL if the lesions are resectable [338, 339]. In cases of BMs without pathological fractures or symptoms of spinal cord compression, radiotherapy can be expected to relieve or eliminate symptoms. A meta-analysis of RCTs regarding the efficacy of radiotherapy for metastatic bone tumors revealed that radiation relieved pain in 61–62% of patients in an intention-to-treat analysis (72–75% in assessable patients) and eliminated pain in 23–24% (28–29% in assessable patients) [340]. In addition to systemic therapy for BM, radiotherapy is recommended for pain relief. Combining bone-modifying agents (BMAs) for bone metastases is expected to delay the onset of skeletal-related events (SREs) such as pathological fractures, spinal cord compression, or radiation or surgery involving bone (see CQ 8-7).

All reports on the resection of metastatic pulmonary tumors have been retrospective studies. An expert consensus on local therapy for metastatic pulmonary tumors by the Society of Thoracic Surgeons Work Force of Evidence Based Surgery stated that: 1) when caring for

patients with cancer and pulmonary oligometastases, pulmonary metastasectomy should be considered within a multidisciplinary team on a carefully individualized basis; 2) pulmonary metastasectomy can be considered with a preference for minimally invasive surgery; 3) although the absolute number of pulmonary metastases does not represent a direct contraindication for pulmonary metastasectomy, candidate selection for pulmonary metastasectomy is best suited to patients harboring three or fewer pulmonary metastases; and 4) stereotactic radiotherapy is a reasonable option for patients with pulmonary oligometastases, particularly for patients considered at high risk in resection or who decline resection [341]. However, no reports have described pulmonary metastasectomy for thyroid cancer.

All reports on local therapy with surgery or radiotherapy for bone or lung metastases from DTC have been exclusively from retrospective studies, mostly from single centers. The efficacy of topical local therapy in addition to internal RAI therapy has been variously described as both practical and ineffective [342–352]. Within the multidisciplinary team, it is important to determine the optimal treatment plan for each patient based on patient condition, symptoms of metastasis, and other recurrence or metastasis.

No reports have clarified patient perspectives regarding local therapy for single or few bone or pulmonary metastases.

CQ 8-6.

Is surgical treatment recommended for cases with spinal metastases (SMs) and spinal compression symptoms or long bone metastases at risk of pathological or impending fracture?

Recommendation statement

Surgical treatment is recommended for cases with SM and spinal compression symptoms or long bone metastases at risk of pathological or impending fracture.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 89%

Outcomes considered

- Health condition from the patient's perspective
- Prognosis (death due to carcinoma)

Evidence

- In some cases, spinal cord compression by BMs causes complete paralysis within a matter of hours. Initiating treatment before irreversible changes can occur is therefore essential.
- Progression of metastases in the long bones can lead to increased cancer-related pain and dysfunction of the affected limb due to impending or pathological fractures.

- Surgical treatment for cases with SM and spinal compression symptoms or long bone metastases at risk of pathological or impending fracture is expected to maintain function and improve QOL.

Summary and discussion of the literature

RAI therapy is the first-line treatment for BM from DTC. RAI therapy should be continued if efficacy is seen in reducing tumor size and relieving symptoms. Other therapies (surgery, radiotherapy, selective embolization, molecularly targeted drugs) may be administered in addition to RAI, depending on the metastatic site, number of metastases, and presence or absence of symptoms. Particularly in patients with solitary BMs, surgery is often combined with RAI therapy where possible. SM and long bone metastases often require urgent treatment because of the potential for significant impacts on QOL due to spinal cord compression symptoms, pathological fractures, or impending fractures that occur with disease progression.

In some cases, spinal cord compression by BMs causes complete paralysis within a matter of hours. Initiating treatment before irreversible changes can occur is therefore essential. Few reports have described surgical therapy for SM due to the limited number of cases and the variety of treatment options available. Patchell *et al.* randomly assigned patients with spinal cord compression caused by metastatic cancer to either surgery followed by radiotherapy ($n = 50$) or radiotherapy alone ($n = 51$) and compared the subsequent ability to walk. After treatment, 84% of patients in the surgery followed by radiotherapy group could walk (42/50), compared to 57% in the radiotherapy-alone group (29/51). This corresponds to an OR of 6.2 (95% CI 2.0–19.8; $p = 0.001$). Patients treated with surgery followed by radiotherapy also retained the ability to walk significantly longer (median, 122 days) than those treated with radiotherapy alone (13 days; $p = 0.003$). Direct decompressive surgery plus postoperative radiotherapy therefore appears superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer [338]. However, surgical therapy is not recommended if more than 48 hours have elapsed since the onset of complete paralysis or if the life prognosis is estimated to be less than 6 months.

Progression of metastases in the long bones can lead to increased cancer-related pain and dysfunction of the affected limb due to impending or pathological fractures. Surgical treatment of such metastases is thus necessary to improve QOL. A multicenter prospective study by Nooh *et al.* reported improved limb function and pain at 2 weeks postoperatively compared to preoperatively, with further improvements over time at 6 weeks, 3 months, 6 months, and 1 year. Improvements in limb

function and pain in the early postoperative period demonstrate the efficacy of surgical management for metastatic long-bone disease at risk of impending or pathological fractures [339].

All reports on the treatment of SM from thyroid cancer have been retrospective in design, mostly from single centers and with a small number of cases. In a retrospective analysis of 202 patients with thyroid cancer and SM, 57% of patients presented with symptoms of neuronal structure compression, including spinal cord compression in 45% and root compression in 12%. In 28% of patients, back pain was an initial symptom. The remaining 15% were asymptomatic. Of the 183 cases with information about treatment for SM, 67% received surgical therapy, 47.5% received external irradiation, and 39% received arterial embolization. By histological type, 72% of 120 cases with SMs from FTC were treated surgically and 18% received conservative treatment; 66% were RAI avid and 34% were refractory. In 54 patients with SMs from PTC, 55% were treated surgically and 28% received conservative treatment. Of these, 43% were RAI avid and 57% were refractory. Due to the varying degrees of SM progression and differences in treatment choices, few studies have compared the effectiveness of each surgical treatment for SM [337]. A study by Jiang *et al.* showed that surgery combined with conservative treatment or total spondylectomy for SMs from DTC did not affect postoperative recurrence or survival. However, curettage and stabilization were shown to effectively relieve pain and improve QOL and neurological status for patients [353]. Meanwhile, Demura *et al.* and Kato *et al.* reported that the surgical technique selected affected local tumor recurrence and prognosis in patients with BM from thyroid tumors. Patients who underwent complete excision survived longer than those with incomplete excision (5-year survival rates: 84% vs. 50%; 10-year survival rates: 52% vs. 8%; $p < 0.01$ each). Both studies concluded that complete surgical resection of thyroid SM, if achievable, can potentially maintain performance status and prolong survival [354, 355]. In a retrospective study of 50 patients with DTC and cervical SMs, Yin *et al.* reported that the 5-year overall survival after diagnosis of cervical SMs was better in the surgery group (44.7%) than in the non-surgery group (11.1%, $p = 0.01$). Surgical intervention was significantly associated with improved survival (HR 0.37, 95%CI 0.14–0.98; $p = 0.04$, multivariate analysis) [356]. Conversely, other studies have reported that surgical therapy did not contribute to improved prognosis [337, 357, 358].

It is important to determine the surgical procedure, including surgical indications for each patient, based on condition, progression of SM or long bone metastases, symptoms of metastasis, and presence of other

recurrences or metastases, as well as the capabilities of the treatment team.

CQ 8-7.

Are bone-modifying agents (BMAs) recommended for cases with BMs?

Recommendation statement

Treatment with BMAs is recommended for cases with BMs due to the ability of these agents to reduce the risk of SREs.

Certainty of evidence: B

Strength of recommendation: Strong; **Consensus rate:** 89%

Outcomes considered

- SREs
- AEs

Evidence

- BMAs delay the onset of SREs
- In terms of AEs, denosumab is associated with a higher frequency of jaw osteonecrosis and hypocalcemia than zoledronic acid. Nephrotoxicity and acute-phase reactions are more common with zoledronic acid.

Summary and discussion of the literature

SREs associated with the progression of BMs can adversely affect activities of daily living, QOL, and prognosis in patients. Avoidance of SREs is thus clinically important. In a study of 245 patients with BMs from DTC, 78% experienced at least one SRE, with an average time of 5 months from diagnosis of BM to first SRE onset. Of these, 65% of patients developed a second SRE, with a median time of 10.7 months from first SRE to second SRE onset. These intervals are very similar to those seen with metastatic breast and prostate cancers [359].

No RCTs have examined the effects of BMAs on patients with bone metastasis from DTC [360]. In a phase III, double-blinded RCT of SMs in patients with lung cancer and other solid tumors, zoledronic acid significantly increased time to first SRE compared to placebo. This treatment significantly reduced the risk of developing multiple SREs, a secondary endpoint [361]. Further, a randomized, double-blinded study of denosumab *versus* zoledronic acid in the treatment of BMs in patients with advanced cancer (excluding breast and prostate cancers) or multiple myeloma demonstrated no difference in OS or disease progression. However, the non-inferiority of denosumab compared with zoledronic acid was seen in terms of delaying the time to first on-study SRE [362]. In a subanalysis of that study, denosumab was seen to significantly delay the time to first SRE or malignancy-associated hypercalcemia by 4.6 months (Kaplan–Meier estimates: median 19.0 months

for denosumab *versus* 14.4 months for zoledronic acid; HR 0.83, 95%CI 0.71–0.97; $p = 0.022$). Denosumab also significantly reduced the hazard of requiring radiation therapy to bone by 22% (HR 0.78, 95% CI 0.63–0.97, $p = 0.026$). [363]. AEs were generally similar, but the frequencies of hypocalcemia and osteonecrosis of the jaw were higher among patients treated with denosumab, and nephrotoxicity and acute-phase reactions were more common in patients treated with zoledronic acid [364–366].

CQ 8-8.

Is local therapy recommended for cases with brain metastases?

Recommendation statement

Local therapies such as surgical resection, stereotactic radiotherapy, and whole-brain radiotherapy are recommended for cases with brain metastases.

Certainty of evidence: B

Strength of recommendation: Strong; **Consensus rate:** 89%

Outcomes considered

- Prognosis
- AEs
- Health condition from the patient's perspective

Evidence

- All reports on the treatment of brain metastases from thyroid cancer have been retrospective studies.
- The 1- and 2-year OS rates for DTC cases with brain metastases ranged from 28% to 68.2% and from 30.2% to 45.5%, respectively.
- Surgical resection or stereotactic radiotherapy is often the treatment for brain metastases, and many reports have indicated that prognosis is better in the treated group than in the untreated group.
- Whole-brain radiotherapy does not prolong survival, but reduces the local recurrence rate and the incidence of new lesions.
- Few brain metastases show uptake of RAI. Even if RAI uptake is present, RAI therapy should be avoided because of the high risks of cerebral edema and hemorrhage.

Summary and discussion of the literature

The frequency of brain metastases in patients with DTC is low, ranging from 0.15% to 1.5%; approximately 60% of patients with brain metastases show concurrent pulmonary metastases [367, 368]. The treatment strategy should consider the presence and control of the primary tumor and other metastatic lesions, the general condition and age of the patient, and the status of the brain metastases.

All reports on the treatment of brain metastases from thyroid cancer have been retrospective studies, mostly

from single centers with a small number of cases. According to 14 references collected, 1- and 2-year overall survival rates ranged from 28% to 68.2% and from 30.2% to 45.5%, respectively [367-380]. Treatment options include surgery, stereotactic radiotherapy, whole-brain radiotherapy, chemotherapy, molecularly targeted therapy, and RAI therapy alone or in combination. Surgery and stereotactic radiotherapy are the most common choices, and patients selected to receive these two treatments have been reported to achieve longer survival than those receiving other treatments. Stereotactic radiotherapy has recently become more common.

Since evidence is lacking regarding the treatment of brain metastases from thyroid cancer, treatment options should be similar to those for metastatic brain tumors in adults. Treatment options for metastatic brain tumors include surgery, stereotactic radiotherapy, and whole-brain radiotherapy. The RPA (Recursive Partitioning Analysis) and GPA (Graded Prognostic Assessment), both used as prognostic indicators, include Karnofsky Performance Status, patient age, number of brain metastases, presence of extracranial metastases, and control of the primary tumor [381]. The condition and age of the patient at the time of treatment are essential factors in determining treatments for brain metastases.

Treatment strategies for brain metastases vary according to the site, number, and size of metastases. When fewer than four brain metastases are present, tumor resection is recommended for metastases larger than 3 cm in diameter at resectable sites. In contrast, stereotactic radiotherapy or surgery is recommended for lesions smaller than 3 cm. Whole-brain radiotherapy is recommended when five or more metastases are evident. However, in some instances with ten or fewer lesions present at a total volume of 15 mL or less, stereotactic radiotherapy with careful follow-up and salvage therapy represents another treatment option [382-385].

Although whole-brain radiotherapy is the standard treatment for multiple brain metastases, cognitive decline has been reported at 3–4 months after irradiation. Moreover, adding whole-brain radiotherapy after stereotactic radiotherapy or surgery reduces local recurrence and the appearance of new lesions, but does not prolong survival [386-390].

RAI for brain metastases should be avoided because few metastatic lesions in the brain show uptake of RAI. Even if RAI uptake occurs, serious complications such as cerebral edema and cerebral hemorrhage may result [372]. No reports have clarified patient perspectives regarding local therapy for brain metastases of DTC.

Chapter 9. Pharmacotherapy for thyroid cancer

Clinical algorithm 9-1. Molecularly targeted therapies for RAI-refractory, metastatic/recurrent DTC (Fig. 12)

Clinical algorithm 9-2. Molecularly targeted therapies for advanced/metastatic/recurrent MTC (Fig. 13)

Clinical algorithm 9-3. Molecularly targeted therapies for unresectable ATC (Fig. 14)

Column 9-1: Immune checkpoint inhibitors for thyroid cancer

Since the efficacy of the anti-CTLA-4 antibody ipilimumab, an immune checkpoint inhibitor, was demonstrated for malignant melanoma [391], the efficacy of anti-PD-1/PD-L1 antibodies has been confirmed in various types of cancer. Such agents are now used in clinical practice not only for malignant melanoma, but also for lung cancer, head and neck cancer, esophageal cancer, gastric cancer, breast cancer, liver cancer, renal cell carcinoma, urothelial cancer, cholangiocarcinoma, endometrial cancer, cervical cancer, and other malignancies. One reason immune checkpoint inhibitors have changed the concept of anticancer drugs is their ability to exert tumor-agnostic therapeutic effects, as can be inferred from the wide range of indications mentioned above. For example, in solid tumors with a high frequency of microsatellite instability (MSI-High), the anti-PD-1 antibody pembrolizumab has shown a response rate of 53%, regardless of the type of solid tumor (including thyroid cancer) [392]. Similarly, the MSI-High cohort in the KEYNOTE-158 trial demonstrated efficacy from pembrolizumab regardless of tumor type [393], leading to pembrolizumab being approved for insurance coverage for “unresectable advanced or recurrent solid tumors with high-frequency microsatellite instability (MSI-High) (limited to cases where standard treatment is difficult)”. Further, in the KEYNOTE-158 trial, the relationship between tumor mutation burden (TMB) and therapeutic effect of pembrolizumab was examined, showing a response rate of 29% in TMB-High (≥ 10 mutations/ megabase [Mgb]) cases regardless of tumor type (including thyroid cancer), compared to 6% in non-TMB-High (< 10 mutations/Mgb) cases [394]. Based on these results, pembrolizumab was also approved for insurance coverage for “advanced or recurrent solid tumors with high tumor mutation burden (TMB-High) that have worsened after cancer chemotherapy (limited to cases where standard treatment is

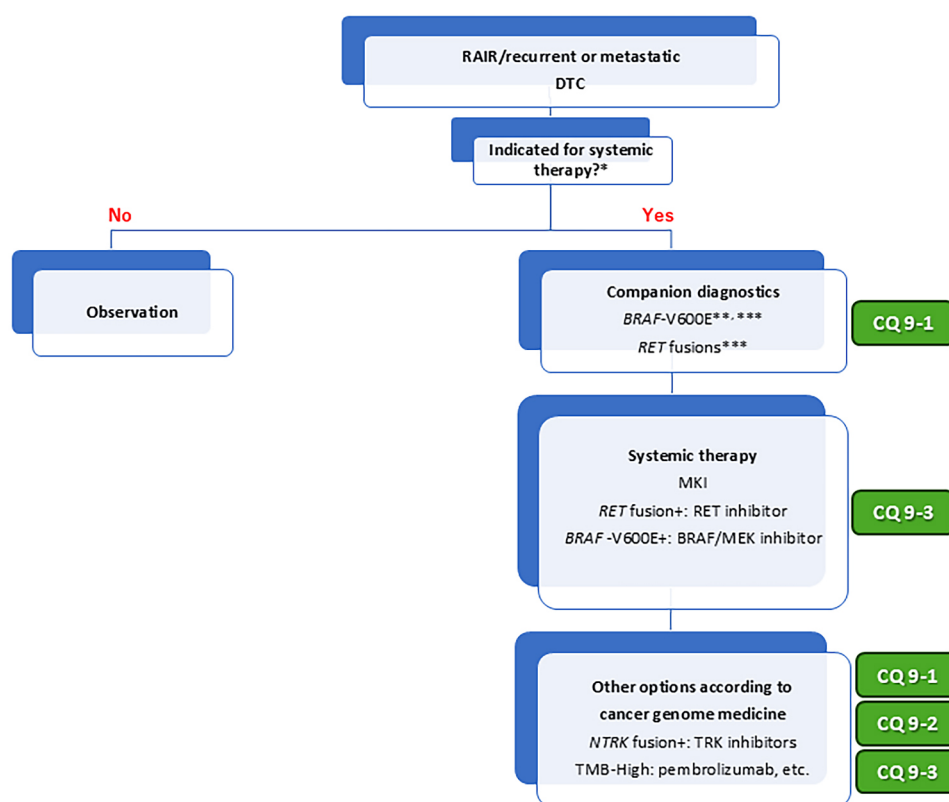


Fig. 12 Clinical algorithm 9-1. Molecularly targeted therapy for radioactive iodine (RAI)-refractory, metastatic/recurrent differentiated thyroid carcinoma (DTC)

*Condition of the patient, such as speed of progression, tumor burden and symptomatic disease, should be carefully considered.

**MEBGEN™ BRAF3 Kit

***OncomineDxTT multi-CDx

RAIR-DTC: radioactive iodine-refractory differentiated thyroid cancer; MKI: multi-targeted kinase inhibitor.

difficult)". Understanding the potential availability of treatment options for thyroid cancer patients, beyond the traditional treatment indications by cancer type, is extremely important for proposing appropriate treatment options to patients. However, the frequency of MSI-High in thyroid cancer is only around 2–3% [392], and the frequency of TMB-High is also reported as 2.7%, highlighting the challenge of efficiently identifying the few eligible patients by utilizing cancer genomic medicine (see Note 8-1).

On the other hand, prospective trials of immune checkpoint inhibitors specifically targeting thyroid cancer remain limited. In DTC, the safety and efficacy of pembrolizumab in PD-L1-positive advanced or metastatic PTC/FTC ($n = 22$) were reported in the KEYNOTE-028 Phase Ib trial. About 80% of patients had received RAI therapy, and approximately 70% had undergone some form of systemic therapy. The response rate was 9% [395]. Further, in the thyroid cancer cohort of the KEYNOTE-158 multi-cohort Phase II trial, the efficacy and safety of pembrolizumab were evaluated in patients with PTC/FTC ($n = 103$) who were refractory to

or intolerant of standard treatment, regardless of PD-L1 expression. The response rate was 6.8%, including 8.7% in PD-L1-positive cases and 5.7% in PD-L1-negative cases, showing no significant difference in response rate based on PD-L1 expression. In terms of safety, about 5% of patients experienced Grade 3 or higher immune-related AEs (colitis, liver dysfunction, adrenal insufficiency, lung disorders, type 1 diabetes), similar to previous trials, with no new safety concerns identified [396].

Based on these results, given the indolent nature of DTC, identification of biomarkers (including MSI-High or TMB-High) that correlate with the efficacy of immune checkpoint inhibitors seems necessary to appropriately narrow down the target population.

In ATC, some reports have indicated a higher tumor mutation burden compared to DTC and PDTC [200], and systematic reviews have reported an MSI-High rate of 7.4% [397]. Since this highly aggressive disease has limited treatment options and poor prognosis, immune checkpoint inhibitors are expected to have a role to play. However, prospective trials for this rare disease are

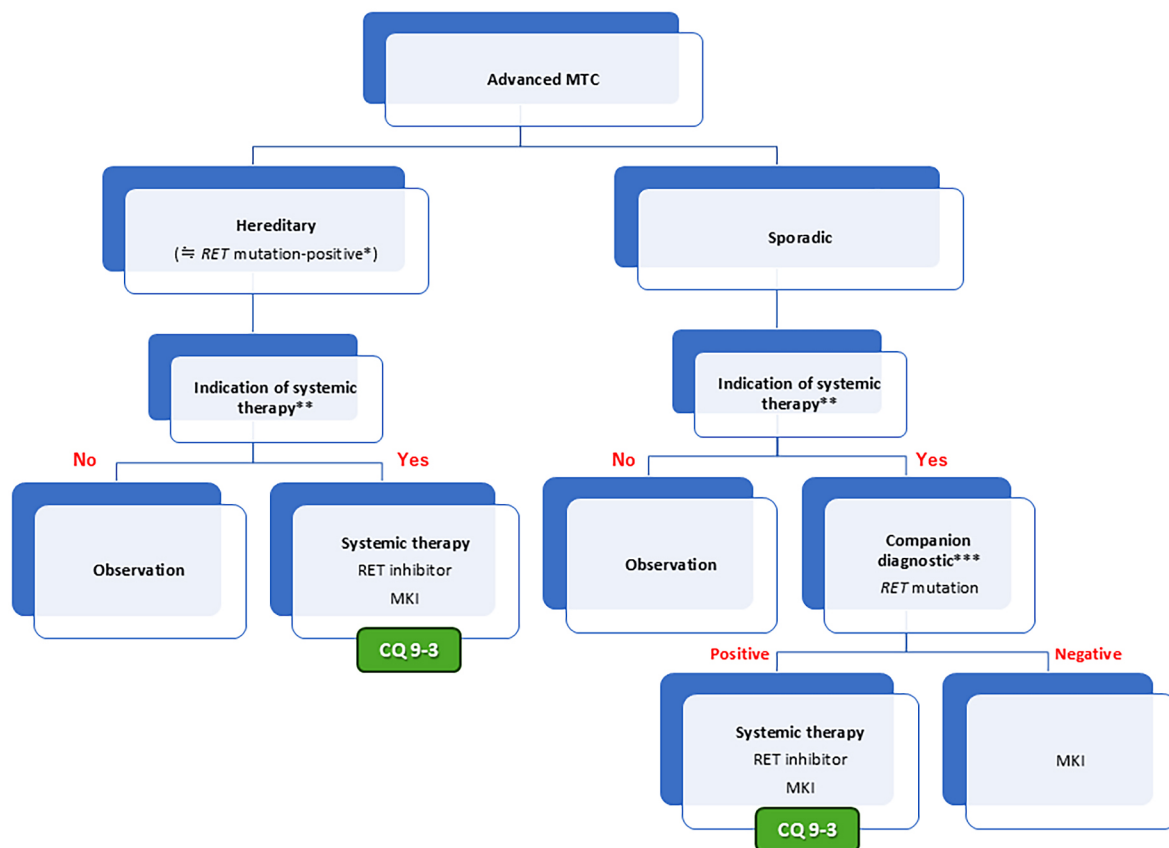


Fig. 13 Clinical algorithm 9-2. Molecularly targeted therapy for advanced/metastatic/recurrent medullary thyroid carcinoma (MTC)

*Gene test for germline *RET* mutation

**Condition of the patient, such as speed of progression, tumor burden and symptomatic disease, should be carefully considered.

*** OncomineDxTT multi-CDx

MKI: multi-targeted kinase inhibitor.

understandably scarce. The only study reported in the literature so far is a Phase II trial of spartalizumab, an anti-PD-1 antibody, for ATC in 42 patients [398]. In that trial, the response rate was 19%, with 29% among PD-L1-positive cases and 0% among PD-L1-negative cases. Response was observed regardless of *BRAF* mutation status, and the 1-year survival rate was 40%. These results highlight potential for further development of immune checkpoint inhibitors in the treatment of ATC. Indeed, a Phase II trial (NCT05696548) evaluating the efficacy of nivolumab and lenvatinib is currently underway in Japan.

As mentioned above, immune checkpoint inhibitors are not entirely uninvolved in the field of thyroid cancer. A key challenge lies in how effectively treatment options can be proposed to patients and how immune-related AEs (irAEs) that arise from the use of these agents can be managed. The development of useful treatment options requires the establishment of an environment that facilitates cancer genomic medicine. Equally important is the development of systems that can accurately diag-

nose and treat irAEs affecting various organs (Table 15). We are no longer in an era where cancer treatment can be handled by a single department. Strengthening collaborations both within and outside medical institutions is crucial.

Note 9-1: What is cancer genomic medicine?

With the rapid spread of next-generation sequencing (NGS), comprehensive detection of multiple gene alterations related to the development and progression of malignant tumors has become possible using gene panel tests. Along with this, the infrastructure for conducting comprehensive genome profiling (CGP) tests under insurance coverage has been established, and these methods were included under insurance coverage in June 2019. Currently available CGP tests include the following five types: “OncoGuide NCC Oncopanel”, “FoundationOne CDx”, “GenMineTOP Cancer Genome Profiling System” using tumor tissue specimens, and “FoundationOne Liquid CDx” and “Guardant360 CDx” using circulating tumor DNA derived from tumor cells present in the blood.

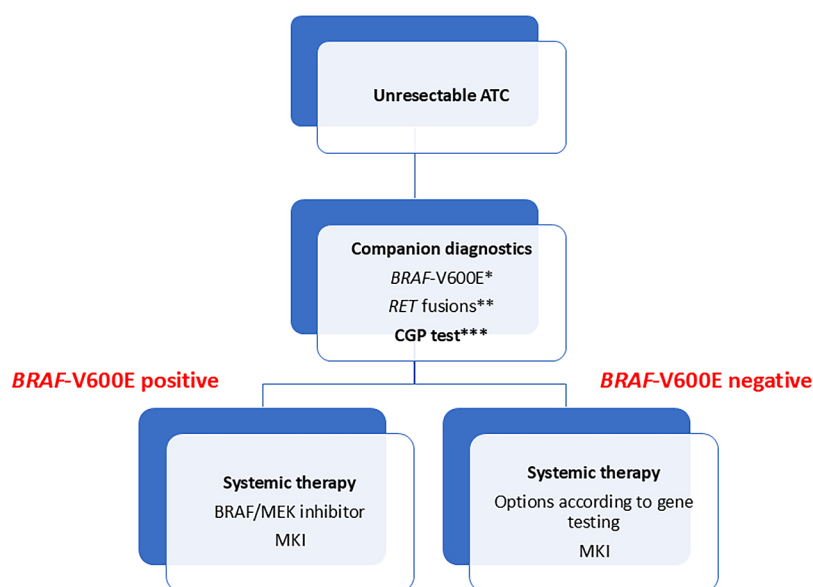


Fig. 14 Clinical algorithm 9-3. Molecularly targeted therapy for unresectable anaplastic thyroid carcinoma (ATC)

*MEBGEN™ BRAF3 Kit

**Oncomine DxTT multi-CDx

***Comprehensive genome profiling (CGP) test

MKI: multi-targeted kinase inhibitor.

Table 15 Immune-related adverse events caused by immune checkpoint inhibitors

Organs	Immune related adverse events
Skin	Skin toxicities (pruritus, rash, vitiligo, <i>etc.</i>)
Endocrine	Thyroid dysfunction, hypophysitis, adrenal insufficiency, type 1 diabetes
Lung	Interstitial lung disease
Liver	Liver dysfunction, cholangitis
Intestine	Diarrhea, colitis
Kidney	Kidney dysfunction (interstitial nephritis)
Hematology	Cytopenia
Neuromuscular	Peripheral neuropathy, encephalitis, myasthenia gravis, myositis
Heart	Myocarditis, pericarditis

1) What are CGP tests?

The purpose of CGP tests is twofold: first, to provide genome profiling of changes in over 100 cancer-related genes to identify the characteristics of a targeted malignancy; and second (and more importantly in the clinical setting), to estimate the effectiveness of antitumor drugs based on the detected gene alterations and to identify clinical trials for which the patient may be eligible. These tests are intended for “patients with solid tumors for which there is no standard treatment, or those with locally advanced or metastatic solid malignancies who have completed standard treatment (including those expected to complete it)”. As of July 2023, these tests can only be conducted at 13 cancer genomic medicine-

designated core hospitals, 32 cancer genomic medicine-designated hospitals and 203 cancer genomic medicine cooperative hospitals across Japan [399]. The return of CGP test results requires detailed review by an expert panel, taking around 4–8 weeks in many facilities. Facilities conducting CGP testing must therefore carefully determine what constitutes the standard treatment for each cancer type, ensuring that testing is performed at the appropriate time to avoid missing opportunities to submit samples, particularly for patients with advanced malignancies. In addition, the treatment-match rate for solid malignancies, in which testing is used to explore treatment options after standard treatments, is reported as 7.7% [400]. However, in thyroid cancer, the likelihood of

gene alterations linked to therapeutic drugs such as the *BRAF*, *RET*, and *NTRK* genes is relatively high. Moreover, there is the advantage of simultaneously conducting microsatellite instability (MSI) testing to determine insurance coverage for immune checkpoint inhibitors, as well as measuring TMB. Thus, when used in combination with the companion diagnostics mentioned later, these tests can be effectively utilized in the treatment of thyroid cancer.

2) What are companion diagnostics (CDx)?

In the field of thyroid cancer, CDx have emerged to determine the applicability of therapies tied to specific genetic abnormalities. One such diagnostic is the “Oncomine Dx Target Test Multi CDx System (ODxTT)”, which detects whether a patient has *RET* fusion-positive thyroid cancer or *RET* mutation-positive medullary thyroid cancer, to determine eligibility for administration of the *RET* inhibitor selpercatinib, and whether a patient has *BRAF*-V600E mutation-positive thyroid cancer, to determine eligibility for the combination of a *BRAF* inhibitor plus MEK inhibitor, namely encorafenib plus binimetinib [401, 402]. Like the previously mentioned CGP tests, this system uses NGS technology to simultaneously analyze 46 cancer-related genes. However, as CDx for thyroid cancer, only the presence or absence of *RET* and *BRAF* gene alterations is reported, and the remaining information is not available for clinical practice. The advantages of CDx include: 1) there are no limitations on where testing can be performed; 2) since the effectiveness and safety of the drug tied to CDx have already been sufficiently validated during the approval process, no expert panel is required; and 3) test results are returned quickly (within 1–2 weeks). Drawbacks, as mentioned earlier, include the fact that information other than *RET* and *BRAF* gene abnormalities are only available for research purposes and cannot currently be applied in clinical practice.

3) Challenges with CGP tests and CDx

As described above, while both test types utilize comprehensive genetic analysis with NGS technology, CGP tests explore “whether there are any therapeutic drugs or clinical trials corresponding to detected genetic alterations”, while CDx “identify genetic alterations linked to specific therapeutic drugs”. Understanding this distinction along with the differences in insurance coverage is crucial for effective application of the tests to clinical practice. For example, if sufficient tumor tissue is available, the Oncomine Dx Target Test (ODxTT) can be performed first. Even if the patient tests negative for *RET* fusion genes/mutations or *BRAF* V600E, CGP testing can then be requested if the patient is being treated with existing multi-target tyrosine kinase inhibitors and is expected to complete standard treatment. When tumor

tissue is scarce or outdated, more strategic planning is required, giving consideration to factors such as age at onset and histological type of the tumor, and assessing which genetic alterations are most likely to be detected. This will guide whether CDx such as the ODxTT or CGP test should be prioritized. Moreover, in thyroid cancer, multiple genetic alterations associated with treatment, so the approval of future therapeutic drugs and related CDx represents a significant issue. For example, the *BRAF* V600E mutation is observed in approximately 60% of PTCs and 10–50% of ATCs, and the efficacy of *BRAF* inhibitors or combined *BRAF*/MEK inhibitors has been demonstrated [403, 404]. On November 24, 2023, the combination of dabrafenib and trametinib was approved for *BRAF*-mutant solid malignancies as a tumor-agnostic indication in Japan. To determine eligibility for this treatment, the companion diagnostic MEBGEN™ *BRAF*3 kit must be used to detect the presence of the *BRAF* V600E mutation. Even if *BRAF* V600E mutation is detected through ODxTT, combined therapy with dabrafenib plus trametinib cannot be prescribed without a result from the MEBGEN™ *BRAF*3 kit and only encorafenib plus binimetinib can be applied. Therefore, when considering therapies linked to common genetic alterations in thyroid cancers, establishing a system for drug development and approval that minimizes the need for multiple tests is crucial to reduce the burden on patients.

CQ 9-1.

Are cancer gene tests recommended for patients with recurrent or metastatic thyroid cancer?

Recommendation statement

There is a possibility of detecting genetic alterations linked to molecularly targeted agents with confirmed efficacy and safety, such as *BRAF* V600E gene mutation, *RET* gene mutation/fusions, and *NTRK* fusions. Cancer gene testing is therefore recommended.

Certainty of evidence: B

Strength of recommendation: Strong; **Consensus rate:** 100%

Outcomes considered

- Outcomes of benefit: improved survival, improved progression-free survival, improved QOL and reduced toxicities associated with treatment
- Outcomes of harm: delays in treatment initiation due to testing, potential identification of incidental findings

Evidence

- For *BRAF* V600E mutation-positive advanced thyroid cancer (particularly PTC and ATC), the efficacy and safety of treatment with *BRAF* inhibitors or a combination of *BRAF* inhibitors and MEK inhibitors have been demonstrated [402–408].
- For *RET* mutation-positive MTC and *RET* fusion-positive

thyroid cancer, the efficacy and safety of RET inhibitors have been shown [401, 409, 410].

- For *NTRK* fusion-positive thyroid cancer, the efficacy and safety of TRK inhibitors have been confirmed [411, 412].
- In addition, in solid tumors, including thyroid cancer, with microsatellite instability (MSI-High) or high tumor mutational burden (TMB-High; ≥ 10 mutations/Mb), the efficacy and safety of anti-PD-1 antibodies have been demonstrated [392-394].

Summary and discussion of the literature

As stated in Note 9-1, with the rapid proliferation of NGS in recent years, cancer gene panel tests that comprehensively detect multiple gene alterations related to cancer development and progression have become available. The cancer gene panel tests used to confirm cancer-related gene alterations in this CQ include so-called CGP tests used in cancer genome medicine, as well as hotspot panel tests and polymerase chain reaction (PCR) tests used as CDx, such as the ODxTT and the MEBGEN™ BRAF3 Kit, which was newly approved in November 2023.

Thyroid cancer shows a high frequency of gene alterations that can be targeted for treatment. Analysis using The Cancer Genome Atlas (TCGA) has shown that approximately 60% of PTCs harbor the *BRAF* V600E mutation, and 12% of thyroid cancers contain some form of fusion gene [413, 414]. *RET* fusion genes, such as *CCDC6-RET* and *NCOA4-RET*, are predominantly found in PTCs, though frequencies vary. The aforementioned

TCGA analysis reported a frequency of 6.8% in PTCs [413], while recent reports have suggested rates could be as high as 36% [415]. Other reports have indicated a high prevalence in younger patients (37%) [416]. *NTRK* fusion genes are also predominantly found in PTC, with *ETV6-NTRK3* and *TPM3-NTRK1* as representative examples. The reported frequencies of these fusion genes vary, but recent studies have estimate rates around 1–2% [417, 418], and others have suggested a slightly higher prevalences in younger patients [417-419]. In addition, the occurrence of MSI-High or TMB-High, as tumor-agnostic indications for the anti-PD-1 antibody pembrolizumab, has been reported to be around 2–3% [392, 420-422].

A summary of prospective studies on the efficacy of BRAF inhibitors and combination treatment with BRAF inhibitors and MEK inhibitors for *BRAF* V600E mutation-positive thyroid cancer is provided in Table 16. Strictly speaking, *BRAF* gene mutations include variants other than *BRAF* V600E, and sensitivities to BRAF inhibitors vary, but in thyroid cancer, the majority are *BRAF* V600E mutations, and the current focus is therefore on this mutation. *BRAF* V600E mutation is found in approximately 40% of ATCs [200], and the high efficacy of combination treatment with BRAF inhibitors and MEK inhibitors provides a crucial treatment option for this highly aggressive cancer type with poor prognosis (see CQ 9-4). Similarly, since a certain level of efficacy has also been shown in *BRAF* V600E mutation-positive DTC (see CQ9-3-1), checking for the presence of the

Table 16 Selective kinase inhibitors for recurrent or metastatic thyroid cancer

Treatment	N	Patient	ORR	PFS
Dabrafenib + trametinib	36	<i>BRAF</i> -V600E-mutated ATC	56%	6.7 months
Dabrafenib + trametinib	27	<i>BRAF</i> -mutated DTC	48%	15.1 months
Encorafenib + binimetinib	17	<i>BRAF</i> -V600-mutated DTC	47%	79% (1 year)
	5	<i>BRAF</i> -V600-mutated ATC	80%	75% (1 year)
Selpercatinib	55	<i>RET</i> -mutated MTC (treated)	69%	82% (1 year)
	88	<i>RET</i> -mutated MTC (untreated)	73%	92% (1 year)
	19	<i>RET</i> fusion-positive DTC	79%	64% (1 year)
Selpercatinib vs. vandetanib/cabozantinib	193	<i>RET</i> -mutated MTC (untreated)	69%	87% (1 year)
	98		39%	66% (1 year)
Pralsetinib	55	<i>RET</i> -mutated MTC (treated)	60%	75% (1 year)
	21	<i>RET</i> -mutated MTC (untreated)	71%	81% (1 year)
	9	<i>RET</i> fusion-positive DTC	89%	81% (1 year)
Entrectinib	13	<i>NTRK</i> fusion-positive TC	54%	NA
Larotrectinib	22	<i>NTRK</i> fusion-positive DTC	86%	100% (1 year)
	7	<i>NTRK</i> fusion-positive ATC	29%	17% (1 year)

N: number of patients; ORR: overall response rate; PFS: progression-free survival; ATC: anaplastic thyroid carcinoma; DTC: differentiated thyroid carcinoma; TC: thyroid carcinoma.

BRAF V600E mutation is essential in advanced thyroid cancer when considering anti-cancer therapy, as the findings can play a significant role in determining the treatment strategy.

A summary of prospective studies on the efficacy of RET inhibitors for *RET* mutation-positive MTC and *RET* fusion-positive thyroid cancer is provided in Table 16. As shown, RET inhibitors demonstrate high efficacy. In particular, for *RET* mutation-positive MTC, a Phase III trial comparing the RET inhibitor selpercatinib with multi-targeted kinase inhibitors (MKIs) (vandetanib/cabozantinib) showed that selpercatinib significantly prolonged PFS (HR for disease progression or death 0.28; 95%CI 0.16–0.48; $p < 0.001$) [410]. Checking for the presence of *RET* gene mutations in tumors is therefore important not only in cases of hereditary MTC, but also in sporadic MTC, as is checking for *RET* fusion genes in advanced thyroid cancers, particularly PTC.

A summary of prospective studies on the efficacy of TRK inhibitors for *NTRK* fusion-positive thyroid cancer is provided in Table 16. As shown, TRK inhibitors exhibit high efficacy. Checking for the presence of *NTRK* fusion genes is important when considering pharmacotherapy for advanced thyroid cancer, particularly PTC, as the findings can play a crucial role in determining treatment strategy.

A Phase II trial of the anti-PD-1 antibody pembrolizumab for MSI-High advanced solid tumors found a response rate of 31% and a median duration of response of 47.5 months, indicating favorable treatment outcomes, and the safety profile was manageable, consistent with results for other anti-PD-1 antibodies [393]. Similarly, pembrolizumab has shown high efficacy in a Phase II trial for advanced solid tumors with mismatch repair deficiency [392]. Further, a Phase II trial of pembrolizumab for TMB-High advanced solid tumors observed a higher response rate (29%) compared to that in non-TMB-High patients (6%) [394]. Although those clinical trials only included a small number of thyroid cancer patients, responses were observed. In cases of advanced thyroid cancer where standard treatment is difficult, confirming MSI-High or TMB-High status can be crucial for determining the treatment strategy.

In conclusion, potential exists for detecting gene alterations such as *BRAF* V600E mutations, *RET* mutations/fusion genes, and *NTRK* fusion genes associated with molecularly targeted therapies offering demonstrated efficacy and safety. Cancer gene tests are therefore recommended for patients with recurrent or metastatic thyroid cancer.

CQ 9-2.

Is second-line treatment with MKIs recommended for

patients with RAI-refractory -DTC that is negative for driver gene alterations?

Recommendation statement

Prescription of MKIs is suggested for patients with RAI-refractory DTC that is negative for driver gene alterations.

Certainty of evidence: B

Strength of recommendation: Weak; **Consensus rate:** 63%

Outcomes considered

- Outcomes of benefit: tumor regression, improvements in QOL, PFS and survival
- Outcomes of harm: adverse reactions related to MKIs

Evidence

- Retrospective studies have reported potential for response and improved prognosis with salvage treatment using MKIs in patients with RAI-refractory DTC, particularly those previously treated with sorafenib or lenvatinib, compared to those who did not receive salvage treatment [423–426]. On the other hand, other reports have indicated a lack of response to salvage treatment with MKIs, making the contribution of MKI-based salvage therapy unclear [427, 428].
- In prospective studies, several single-arm trials have reported that MKIs, including lenvatinib and cabozantinib, demonstrated efficacy in patients with MKI-pretreated RAI-refractory DTC [429–432]. Further, the SELECT trial, as a Phase III study targeting RAI-refractory DTC, included MKI-pretreated cases primarily treated with sorafenib, and lenvatinib showed a significant improvement in PFS compared to placebo, regardless of prior treatment status (HR 0.20 for treatment-naïve cases, HR 0.22 for pretreated cases) [433]. In addition, in the Phase III COSMIC-311 trial comparing cabozantinib with placebo in patients with MKI-pretreated RAI-refractory DTC, cabozantinib showed a significant improvement in PFS compared to placebo (HR 0.22; 96%CI 0.13–0.36; $p < 0.0001$) [434].

Summary and discussion of the literature

The standard first-line treatment for RAI-refractory DTC without driver gene mutations or fusion genes is lenvatinib or sorafenib, based on the results of previous Phase III trials [433, 435]. Both of these agents are MKIs with inhibitory effects primarily on VEGF receptors. For second-line treatment of patients without driver gene mutations or fusion genes, the use of an MKI not previously administered should be considered. Currently, the MKIs with confirmed efficacy against thyroid cancer predominantly inhibit VEGF receptors, but lenvatinib also has inhibitory effects on PDGFR, FGFR, RET, and KIT, while sorafenib has inhibitory effects on PDGFR, RET, and RAF [433, 435]. Theoretically, sequential use

of different types of MKIs may provide clinical benefits.

Findings from previous retrospective studies have suggested that salvage treatment with MKIs improves prognosis compared to no salvage treatment, particularly in RAI-refractory DTC patients previously treated with sorafenib or lenvatinib [423–426]. However, other studies have indicated a lack of response to MKI-based salvage treatment, leaving the contribution of MKI salvage therapy unclear [427, 428]. The efficacy of sequential MKI therapy in MKI-pretreated cases has also been investigated in prospective studies. For example, several single-arm prospective trials have reported the efficacy of MKIs such as lenvatinib and cabozantinib against MKI-pretreated RAI-refractory DTC [429–432]. The SELECT trial, as a Phase III study targeting RAI-refractory DTC, included patients pretreated with MKIs (primarily sorafenib), and found that lenvatinib achieved significant improvements in PFS compared to placebo, regardless of treatment status, with an HR of 0.20 (95%CI 0.14–0.27) for treatment-naïve patients and 0.22 (95%CI 0.12–0.41) for previously treated patients [433]. In addition, the Phase III COSMIC-311 trial compared cabozantinib with placebo in MKI-pretreated RAI-refractory DTC patients, with approximately 30% of participants previously treated with sorafenib, 30% with lenvatinib, and 30% with both. Cabozantinib achieved significant improvements in PFS compared to placebo (HR 0.22; 96%CI 0.13–0.36; $p < 0.0001$) [434].

In conclusion, prescription of MKIs is suggested for RAI-refractory DTC patients who are negative for driver gene alterations. However, the only MKIs available in Japan for use against RAI-refractory DTC are lenvatinib and sorafenib. Cabozantinib, which has the most definitive data, has not yet been approved for thyroid cancer. In addition, no prospective studies have reported the efficacy of sorafenib in patients pretreated with lenvatinib. The strength of this recommendation is thus classified as “weak”.

CQ 9-3-1.

Are selective kinase inhibitors (SKIs) recommended as first-line treatment for RAI-refractory DTC patients who are positive for driver gene alterations?

Recommendation statement

Prescription of SKIs is suggested as first-line treatment for RAI-refractory DTC patients who are positive for driver gene alterations.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 88%

CQ9-3-2.

Are RET inhibitors recommended as first-line treat-

ment for patients with *RET*-mutated recurrent or metastatic MTC?

Recommendation statement

Prescription of a RET inhibitor as first-line treatment is recommended for patients with *RET*-mutated recurrent or metastatic MTC.

Certainty of evidence: B

Strength of recommendation: Strong; **Consensus rate:** 100%

Outcomes considered

- Outcomes of benefit: tumor regression, improvements in QOL, PFS and survival
- Outcomes of harm: AEs

Evidence

- Limited prospective trial data is available regarding the use of BRAF inhibitors/MEK inhibitors for *BRAF* V600E-positive RAI-refractory DTC. In a randomized Phase II trial of 53 patients comparing dabrafenib with dabrafenib plus trametinib, combination therapy in 27 patients demonstrated a response rate of 48% using modified RECIST (30% using RECIST 1.1), with a safety profile consistent with previous reports [403, 404, 406]. Dose reduction due to toxicity was required in 56% of patients, and treatment discontinuation was needed in 22% [403].
- A Phase II trial conducted in Japan on combination therapy with encorafenib plus binimetinib for 22 patients included 17 patients with *BRAF* V600E-positive DTC. Among those 17 patients, 82% had been previously treated with RAI, and 94% had previously received MKIs. The response rate was 47% and the safety profile was consistent with previous reports [402, 436–438]. Dose reduction due to toxicity was required in 14% of patients, and treatment discontinuation was needed in 18%.
- The efficacy and safety of the selective RET inhibitor selpercatinib have been demonstrated both in 55 cases previously treated with vandetanib or cabozantinib, and in 88 treatment-naïve cases of patients with advanced *RET* mutation-positive MTC [401]. Similarly, the efficacy of this agent has been confirmed for advanced *RET* fusion-positive thyroid cancer ($n = 19$).
- In treatment-naïve patients with *RET* mutation-positive MTC, a Phase III trial comparing the RET inhibitor selpercatinib with MKIs (vandetanib/cabozantinib) showed that selpercatinib significantly prolonged PFS (HR for disease progression or death 0.28; 95%CI 0.16–0.48; $p < 0.001$) [410].
- For patients with advanced *NTRK* fusion-positive thyroid cancer, the efficacy and safety of the selective TRK inhibitors entrectinib and larotrectinib have been reported. An integrated analysis of entrectinib ($n = 121$) included thyroid cancer patients ($n = 13$) who

demonstrated similar efficacy to the overall population [411, 439]. Dose reduction due to toxicity was required in 25% of patients, and treatment discontinuation was needed in 8% [439]. Regarding larotrectinib, an integrated analysis of 159 patients that included 26 thyroid cancer patients [440, 441] and an analysis specifically for 29 thyroid cancer patients alone have been reported [412]. Efficacy was comparable in both the overall population and the thyroid cancer subgroup. Dose reduction due to toxicity was required in 8% of patients, with treatment discontinuation needed in 2% [441].

Summary and discussion of the literature

To date, based on the results of SELECT and DECISION randomized trials, the MKIs lenvatinib and sorafenib, which primarily inhibit VEGF receptors, are recognized as standard treatment options for RAI-refractory DTC [433, 435]. Similarly, for advanced MTC, the results of the ZETA and EXAM RCTs have established vandetanib and cabozantinib (not approved for this indication in Japan) as standard treatment options [442, 443]. However, due to the characteristic toxicities associated with MKIs (including hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome (PPES), and rash), dose reductions or discontinuations are sometimes necessary, making proper management of AEs crucial (Table 17) [433, 435, 442, 443]. In contrast, SKIs tend to show a lower frequency of dose reductions or discontinuations due to toxicity compared to MKIs, indicating higher safety and tolerability (Table 17) [401–403, 411, 439, 441]. Both MKIs and SKIs have demonstrated sufficient efficacy, and the choice of which to prioritize as first-line treatment should be determined based on the clinical trial results for each drug, while also considering toxicity and tolerability.

The results of RCTs directly comparing MKIs with SKIs have only been reported for patients with RET-mutated advanced or recurrent MTC. In the LIBRETTO-531 Phase III trial comparing selpercatinib with cabozantinib or vandetanib with a primary endpoint of PFS determined by blinded independent committee review, selpercatinib was shown to significantly prolong PFS (HR for disease progression or death 0.28; 95%CI 0.16–0.48; $p < 0.001$). Further, selpercatinib was less likely to result in dose reductions (39% vs. 77%) or discontinuations (5% vs. 27%) due to AEs, and was therefore considered superior to cabozantinib/vandetanib in terms of safety [410, 444]. For this reason, the use of selpercatinib is prioritized for patients with RET gene-mutated advanced or recurrent MTC who require anti-cancer treatment.

Combination treatment with BRAF inhibitors plus MEK inhibitors for BRAF-V600E-mutated advanced thyroid cancer has been reported mainly for BRAF-V600E-mutated anaplastic thyroid carcinoma [404, 406, 407], and prospective data on BRAF inhibitors plus MEK inhibitors for BRAF V600E-mutated RAI-refractory DTC are scarce. In a randomized Phase II study of 53 patients comparing dabrafenib with dabrafenib plus trametinib for BRAF-mutated RAI-refractory DTC, dabrafenib plus trametinib in 27 patients was reported to have a modified RECIST response rate of 48% (RECIST 1.1: 30%), a median PFS of 15.1 months, and a median OS of 47.5 months. Characteristic AEs included fever, skin disorders, nausea, PPES, and hyperglycemia [403]. A Phase II study of encorafenib plus binimetinib conducted in 22 patients in Japan included 17 patients with BRAF V600E-mutated differentiated cancer, of whom 82% had been previously treated with RAI and 94% had been previously treated

Table 17 Dose reduction and discontinuation due to adverse reactions in MKI and SKIs

Treatment	MKI or SKIs	Dose reduction	Discontinuation
Lenvatinib	MKI	68%	14%
Sorafenib	MKI	65%	19%
Vandetanib	MKI	—	12%
Cabozantinib	MKI	79%	16%
Dabrafenib + trametinib	BRAF/MEK inhibitor	56%	22%
Encorafenib + binimetinib	BRAF/MEK inhibitor	14%	18%
Selpercatinib LIBRETTO-001	RET inhibitor	30%	2%
LIBRETTO-531		39%	5%
Entrectinib	TRK inhibitor	25%	8%
Larotrectinib	TRK inhibitor	8%	2%

MKI: multi-targeted kinase inhibitor; SKI: selective kinase inhibitor.

with MKI. Efficacy in that study was reported as a 47% response rate, 1-year PFS of 79%, and 1-year OS of 77% [402]. Safety was similar to previous studies of melanoma and non-small cell lung cancer [436–438], with characteristic AEs including nausea, PPES, arthralgia, decreased appetite, and serous retinal detachment, but these were manageable with appropriate dose reductions and drug interruptions. In addition, since a certain degree of efficacy has been reported with BRAF inhibitors alone in small-scale prospective studies, BRAF-targeted therapy for *BRAF*-V600E-mutated differentiated cancer is considered promising [403, 405, 408]. In November 2023, based on the results of the ROAR trial, which included 36 cases of ATC and other patients with *BRAF* V600E-mutated advanced solid tumors, as well as the results of the aforementioned randomized Phase II trial for *BRAF*-mutated RAI-refractory DTC, dabrafenib plus trametinib received additional approval in Japan for the treatment of “*BRAF*-mutated advanced or recurrent solid tumors for which standard treatment is difficult” [403, 404, 406, 407].

For advanced MTC with *RET* gene mutations, the efficacy and safety of selpercatinib were analyzed in the Phase I/II LIBRETTO-001 trial, which targeted patients with advanced solid tumors harboring *RET* gene abnormalities [401]. The primary population analyzed included patients previously treated with vandetanib or cabozantinib ($n = 55$), while efficacy and safety were also explored in 88 treatment-naïve patients. Among the 55 pretreated patients, 53% had used two or more types of MKIs, and 60% harbored the *RET* M918T mutation. The results showed a response rate of 69% and a 1-year PFS of 82%. In the treatment-naïve group of 88 patients, 56% were *RET* M918T mutation-positive, with a response rate of 73% and a 1-year PFS of 92%. The efficacy of selpercatinib was also demonstrated in the aforementioned LIBRETTO-531 randomized Phase III trial for treatment-naïve *RET*-mutated MTC [410]. In the LIBRETTO-001 trial, the efficacy and safety of selpercatinib were also explored in patients with *RET* fusion-positive thyroid cancer [401]. Of the 19 patients with advanced *RET* fusion-positive thyroid cancer, 68% had PTC, and 84% had been previously treated with RAI. *RET* fusion genes were predominantly *CCDC6-RET* and *NCOA4-RET*, accounting for approximately 80% of cases. The response rate was reported as 79%, with a 1-year PFS of 64%. Regarding safety, characteristic AEs included dry mouth, hypertension, diarrhea, fatigue, elevated AST, and edema. However, the drug was well tolerated and AEs were manageable with appropriate dose reductions and treatment interruptions. Similarly, the *RET* inhibitor pralsetinib has demonstrated efficacy and safety for both *RET*-mutated MTC and *RET*

fusion-positive thyroid cancer, comparable to those of selpercatinib [409].

For *NTRK* fusion-positive thyroid cancer, 13 thyroid cancer patients were included in an integrated analysis of Phase I and Phase II trials of the TRK inhibitor entrectinib, which targeted 121 patients with advanced solid tumors harboring *NTRK* fusion genes [411, 439]. The response rate for thyroid cancer was 54%, similar to the overall response rate of 61%, with a median PFS of 19.9 months. Characteristic AEs included taste disturbance, dizziness, diarrhea, fatigue, elevated creatinine, and weight gain, but the drug was well tolerated and AEs were manageable with dose reductions and treatment interruptions. Similarly, an integrated analysis has been reported for Phase I and Phase II trials of another TRK inhibitor, larotrectinib, in 159 patients with advanced *NTRK* fusion-positive solid tumors [440, 441]. The overall response rate was 79%, with a median PFS of 28.3 months. An analysis specifically focusing on 29 thyroid cancer patients [412] showed that 22 cases were DTC, 95% had previously received RAI, and 50% had previously been treated with MKIs. Among the fusion genes, *NTRK1* fusion genes accounted for 45%, and *NTRK3* fusion genes accounted for 55%. For the 21 evaluable cases of DTC, the response rate was 86%, with a 1-year PFS of 100%. Characteristic AEs reported in the integrated analysis included fatigue, elevated ALT, cough, anemia, dizziness, and nausea. The drug was well tolerated and AEs were manageable with dose reductions and treatment interruptions [440, 441].

Based on the above results, MKIs are considered the standard treatment for RAI-refractory DTC according to RCTs. However, SKIs have demonstrated high efficacy, safety, and tolerability based on single-arm trials and integrated analyses of single-arm trials. SKIs are thus suggested as an option for first-line therapy in RAI-refractory DTC patients with driver gene mutations or fusions. Notably, combination therapy with dabrafenib and trametinib has received additional approval in Japan for “advanced or recurrent solid tumors with *BRAF* mutations for which standard treatment is difficult” and, based on clinical trial results, is considered a treatment option for patients who have previously been treated with MKIs or for whom MKIs are unsuitable. For *RET*-mutated MTC, the superiority of the SKI selpercatinib over MKIs in terms of PFS, as well as the better safety profile, has been demonstrated in a RCT. Selpercatinib, a SKI targeting *RET*, is therefore recommended as the first-line treatment for advanced or recurrent *RET*-mutated MTC.

CQ 9-4.

Are molecularly targeted agents recommended for

unresectable ATC?

Recommendation statement

1. Prescription of BRAF inhibitors plus MEK inhibitors is recommended for patients with *BRAF* V600E-mutated ATC.

Certainty of evidence: B

Strength of recommendation: Strong; **Consensus rate:** 100%

2. Prescription of SKIs, such as RET inhibitors and TRK inhibitors, is suggested for ATC patients with driver gene alterations other than *BRAF* V600E.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 63%

3. Prescription of lenvatinib is suggested for ATC patients without driver gene alterations.

Certainty of evidence: C

Strength of recommendation: Weak; **Consensus rate:** 63%

Outcomes considered

- Outcomes of benefit: tumor regression, improvements in QOL, PFS and survival
- Outcomes of harm: AEs

Evidence

- For *BRAF* V600E-mutated ATC, high efficacy of combination therapy with BRAF inhibitors plus MEK inhibitors has been demonstrated [402, 404, 406, 407].
- For ATC with other driver gene mutations or fusion genes, responses have been observed in a small number of patients in prospective trials [401, 412].
- Regarding the efficacy of lenvatinib for unresectable ATC, subsequent studies conducted in Japan and overseas have shown lower treatment outcomes compared to results from the initial Phase II trial cohort of 17 patients with ATC reported from Japan [214, 445, 446].
- In prospective trials using other MKIs (pazopanib, sunitinib, sorafenib) for ATC, no cases of response have been observed [447-449].

Summary and discussion of the literature

ATC has an extremely poor prognosis, and no standard systemic therapy has been established. In this challenging context, MKIs, which primarily inhibit VEGF-R, have been developed in recent years. In the past, agents such as pazopanib, sunitinib, and sorafenib were evaluated in Phase II trials, but none showed adequate response [447-449]. On the other hand, lenvatinib, another MKI, demonstrated very promising therapeutic effects in an ATC cohort of 17 patients in a Japanese Phase II trial, with a response rate of 24%, a median PFS of 7.4 months, and a median OS of 10.6 months. As a result, lenvatinib has been approved in Japan for this disease, which has limited treatment options [445]. How-

ever, in subsequent studies, a Phase II trial from the United States ($n = 34$) reported a response rate of only 2.9%, a median PFS of 2.6 months, and a median OS of 3.2 months, leading to study discontinuation due to lack of efficacy. Similarly, a Japanese Phase II trial of 42 patients showed a response rate of 11.9%, with a 1-year PFS of 4.9% and a 1-year OS of 11.9%, representing less favorable outcomes compared to the initial report [214, 445, 446]. Consequently, lenvatinib is now considered a treatment option that should be administered with careful management of the characteristic side effects, as well as a thorough assessment of risks such as bleeding and fistula formation.

On the other hand, approximately 40% of ATCs harbor the *BRAF* V600E mutation [200], and combination therapy with BRAF inhibitors plus MEK inhibitors has been explored. Vemurafenib, a BRAF inhibitor, was evaluated in a basket trial targeting advanced solid tumors with *BRAF* mutations. In the ATC cohort of 7 patients, responses were observed in 2 cases [450]. Subsequently, combination therapy with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib was investigated in the ROAR trial, a basket study for *BRAF* V600E-mutated advanced solid tumors, and the results for the ATC cohort of 36 patients have been reported [404, 406, 407]. The trial demonstrated favorable treatment outcomes, with a response rate of 56%, a median PFS of 6.7 months, and a median OS of 14.5 months [404]. Additionally, a Japanese Phase II trial reported on combination therapy with the BRAF inhibitor encorafenib and the MEK inhibitor binimetinib for *BRAF* V600E-mutated advanced thyroid cancer, including 5 cases of ATC among 22 patients. Responses were observed in 4 of these 5 cases [402]. Based on these results and the robust efficacy and safety data of the combination therapy of BRAF inhibitors plus MEK inhibitors in other *BRAF* V600E-mutated advanced solid tumors, including melanoma, this treatment is strongly recommended for *BRAF* V600E-mutated ATC [402, 404, 436-438, 451-453].

In ATC, driver gene alterations other than *BRAF* V600E mutations are rare. In the Phase I/II trial (LIBRETTO-001) of the RET inhibitor selpercatinib, 2 cases of ATC were included in the RET fusion-positive thyroid cancer cohort, and one case showed response [401]. In addition, in an integrated analysis of larotrectinib for advanced solid tumors with *NTRK* fusion genes, 7 of 29 thyroid cancer cases were ATC, with a response rate of 29%, a median PFS of 2.2 months, and a median OS of 8.8 months [412]. These data suggest the potential efficacy of corresponding SKIs for ATC with driver gene alterations other than *BRAF* V600E, but the number of cases is limited, making it difficult to conduct

comparisons with existing treatment options, including lenvatinib. Prescription of SKIs, such as RET inhibitors and TRK inhibitors, is therefore suggested for ATC patients with driver gene alterations other than *BRAF* V600E.

Chapter 10. Complications and safety management associated with thyroid surgery

Note 10-1. Adverse events (AEs) associated with thyroid surgery

The main AEs associated with thyroid surgery are shown in Table 18. The doctor in charge should explain these AEs to the patient, including the expected frequency, severity, prognosis, and treatment methods before surgery. Considering the problems and values specific to each patient, those AEs with potential for a large impact on postoperative life will be carefully explained. Records of the questions and reactions from the patient should be kept to gauge whether the patient has fully understood.

1) Surgical wounds

The location and length of the wound should be explained. The patient should be informed that the degree and duration of muscle stiffness, tightness, and limited mobility from the neck to the shoulders can vary greatly from person to person, and appropriate stretching and massage should be recommended [83, 454].

2) Dysphonia

Explain that most subjective symptoms, such as hoarseness, difficulty producing high-pitched or loud voices, and shortened speaking time, will likely recover within a few days. It is important to keep in mind that patients are likely to be much more aware of dysphonia than medical professionals would objectively judge. If damage to the RLN or external branch of the superior laryngeal nerve is expected, inform the patient that the recovery period after reconstruction can vary greatly from a few weeks to more than 6 months, and consider

objectively recording the vocal function. It is important to explain in advance the possibility that procedures such as tracheotomy may be needed to secure the airway in an emergency.

3) Swallowing disorders

Early after an operation, patients often experience a feeling of something being stuck in the throat, and difficulty swallowing, but these symptoms generally improve over time.

4) Postoperative bleeding

Although rare, severe bleeding carries a possibility of death by suffocation; the need for emergency measures in such an event should be mentioned.

5) Lymphorrhea

Explain that leakage of lymph (chyle) may occur after lymph node dissection, and that re-operation may be indicated in severe cases or when conservative treatment fails.

6) Hypothyroidism

All patients after total thyroidectomy and a certain percentage after lobectomy will need to take thyroid hormone medications for the rest of their lives to compensate for lost thyroid function.

7) Hypoparathyroidism

Explain the incidence, symptoms and treatment of transient and permanent hypoparathyroidism at your institution.

8) Nerve damage other than laryngeal nerve

Hyposensitivity due to cutaneous nerve paralysis around the wound, especially in the anterior neck and anterior chest, is unavoidable. When performing lateral lymph node dissection, explain the possibility of accessory nerve paralysis that may make raising the affected arm difficult.

9) Wound infection

Although very rare, wound infections due to normal skin flora can occur.

10) Others

When performing mediastinal surgery that requires sternotomy, or when performing extended surgery with

Table 18 Adverse events associated with thyroid surgery that should be explained preoperatively

1. Surgical wound
2. Dysphonia (see CQ9-1, 2 and CQ11-1, 2)
3. Swallowing disorders
4. Postoperative bleeding (see Column 11-1): emergency surgery is necessary to avoid death from suffocation
5. Lymphorrhea
6. Hypothyroidism
7. Hypoparathyroidism (see CQ11-3): explain the frequencies of transient and permanent hypofunction
8. Nerve damage other than laryngeal nerve: cutaneous nerve paralysis and accessory nerve paralysis around the wound, anterior neck and anterior chest
9. Wound infection
10. Others: Postoperative disorders due to extended surgery

concomitant resection of muscles, blood vessels, the trachea, or esophagus other than thyroid gland, it is essential to explain in detail how these procedures will affect QOL after surgery and ensure that both the patient and medical staff are fully convinced of the necessity of the surgery.

These explanations and consents must be given in a written document according to the process established by the hospital.

Note 10-2. Systematic safety management and emergency response required for thyroid surgery

Medical safety cannot be ensured solely through the professional knowledge and technical training of the surgeon. It is essential that the institution establishes and properly operates a systematic safety management to ensure that patients do not suffer disadvantage during thyroid surgery.

1) Examination and equipment useful for reducing complications

Evaluation of vocal cord movement before and after surgery using a laryngoscope and intraoperative nerve monitoring system is recommended to avoid unexpected airway obstruction due to vocal cord paralysis (see CQ 10-1, 2). Appropriate use of hemostatic equipment such as ultrasonic coagulation and bipolar coagulation devices can reduce the amount of bleeding and postoperative drainage, leading to shorter hospital stay.

2) In-facility safety management and education systems

In all facilities that perform thyroid surgery, medical professionals who treat patients should be educated to ensure the safety of patients during the perioperative period, and the entire team should review the procedures for responding to emergencies such as postoperative bleeding and airway obstruction. It is especially desirable to provide medical professionals who may be involved in initial responses with opportunities to participate in training to become familiar with the techniques of surgical airway management (tracheotomy, cricothyrotomy, percutaneous airway management kits).

3) System for responding to emergent unforeseen circumstances

Specific points for observation, frequency of rounds, criteria of doctor calls, *etc.* after surgery should be determined. The establishment of a safety management system should not be undertaken only by the relevant department or ward, but should also be carried out under the director of the facility.

In the event of a medical accident, it is not only the staff providing direct care to the patient who must respond. The medical safety management department of the facility must provide information to every staff mem-

ber and take measures to establish a safety management system on a daily basis based on recent recommendations from the Medical Accident Investigation and Support Center (https://www.medsafe.or.jp/modules/advocacy/index.php?content_id=97).

Column 10-1. How to detect and treat postoperative bleeding

This column proposes a response from the JAES based on suggestions from a report analyzing fatal cases related to airway obstruction due to neck surgery (<https://www.medsafe.or.jp/uploads/uploads/files/teigen16.pdf>). Postoperative bleeding, although rare, can become serious and even fatal if not properly managed. A system for early, reliable detection of postoperative bleeding and rapid, appropriate response must be in place at all facilities performing thyroid surgery.

1) Incidence, timing and risk factors

Postoperative bleeding reportedly occurs in 0.3–2.2% of thyroid surgeries. Mortality due to postoperative bleeding is reported to be as rare as 0–1.3%. This frequency is still much higher than the perioperative mortality rate for all thyroid surgeries (0.01–0.05%) [455–461]. Most postoperative bleeding occurs within 6 hours after surgery and is rare after 24 hours. Risk factors for postoperative bleeding include male sex, surgery for Graves' disease, older age, and obesity. Overconfidence must be strictly avoided, as postoperative bleeding is unrelated to the difficulty of surgery, the extent of resection, or the experience of the surgeon [455–461].

2) Etiologies leading to suffocation

The main cause of suffocation due to postoperative bleeding is not mechanical airway compression by hematoma, but narrowing or obstruction of the airway lumen due to laryngeal edema caused by impaired return of blood flow due to venous compression by the hematoma.

3) Initial symptoms and recommended response

Symptoms and signs include neck swelling (increase in neck circumference), dyspnea (feeling of suffocation), pressure, pain, obstruction (difficulty swallowing saliva), bleeding from the wound, decreased blood pressure, and increased bloody drainage. The speed of progression varies, and the patient becomes obviously restless as the condition worsens. Oxygen saturation drops only when the patient is nearly suffocated. It is essential not to hold back on the initial response. This life-saving procedure should be handled by as many medical professionals as possible.

In cases where symptoms of respiratory distress have already appeared, it is necessary to acknowledge that endotracheal intubation is impossible. The pressure from hematoma must be decompressed by re-opening the

surgical wound, followed by emergency tracheotomy. In some cases, endotracheal intubation is possible if the respiratory status of the patient remains unchanged.

Even after initial measures are successful, airway management must be continued in severe cases until the disappearance of laryngeal edema is confirmed. All medical staff involved with the patient must be informed of the importance of continuing airway management and unification of treatment policy. Progress should be observed objectively using uniform criteria, with treatment decisions made by a multidisciplinary team.

4) Prevention

It is effective to determine a procedure before closing the wound to thoroughly checking that no bleeding is present (*e.g.*, removing blood clots by irrigation, observing for a while, increasing systolic blood pressure, releasing the extended neck position, and increasing venous pressure by the Valsalva maneuver) to reduce the incidence of postoperative bleeding [461]. A system should be established to frequently observe the wound for 24 hours after surgery, and specific postoperative observation items, frequencies, and doctor call criteria should be determined. Objective indicators such as neck circumference should be recorded, and preparations should be made for initial emergency responses. The rarity of events means that repeated education for postoperative bleeding is necessary.

5) Responsibilities of the institution (see Note 10-2)

The director of the institution must take the lead in establishing a medical safety system to ensure smooth coordination between the surgical team and others. Causes of postoperative bleeding are often difficult to determine, and from the perspective of the patient, postoperative bleeding is understood as an emergency for which the patient is not responsible, caused by invasive medical procedures such as surgery. Creating a situation that satisfies both the patient and medical staff is often difficult. Communicating the risks during preoperative explanations is thus essential. Further, it is important to explain the facts sincerely without speculation or excuses in postoperative explanations, and to report to the medical safety department of the facility and consider intervention by a third party. If the outcome is fatal, it is desirable to collect objective records by considering reporting the event as an abnormal death, performing pathological autopsy and postmortem imaging diagnosis, *etc.*, and taking advantage of verification opportunities provided by the Medical Accident Investigation System (Japan Medical Safety Research Organization (medsafe.or.jp)).

CQ 10-1.

Is the use of intraoperative nerve monitoring (IONM)

(intermittent stimulation including the laryngeal twitch technique) recommended during thyroid surgery?

Recommendation statement

The use of IONM is recommended during all thyroid surgeries.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 67%

Outcomes considered

- Frequency of RLN injury
- Frequency of injury to the external branch of the superior laryngeal nerve
- Benefits for the surgeon, such as shortening operation time and reducing stress to identify nerves
- AEs

Evidence

- Previous studies have not statistically confirmed that the use of IONM significantly reduces vocal cord paralysis during thyroid surgery because the incidence of vocal cord paralysis is very low.
- The use of IONM significantly increases the probability of identifying the external branch of the superior laryngeal nerve intraoperatively and increases the likelihood of reducing postoperative dysphonia.
- The use of IONM facilitates identification of the RLN and prediction of postoperative vocal cord paralysis.
- The use of IONM is highly likely to reduce vocal cord paralysis in cases of malignant tumor surgery accompanied by lymph node dissection, cases of large nodular goiter, cases of surgery in which vocal cord paralysis is suspected preoperatively, and cases of reoperation.
- No reports have shown an increased risk of AEs in patients with the use of IONM.

Summary and discussion of the literature

IONM is a method that can check the real-time integrity of a nerve by demonstrating muscle movement in response to nerve stimulation during surgery. Detailed guidelines for IONM use during thyroid surgery have already been published [462, 463]. The incidence of recurrent laryngeal nerve paralysis in thyroid surgery is very low, and a huge number of cases (9 million cases per arm for benign multinodular thyroid tumor surgery and 40,000 cases per arm for thyroid cancer surgery) would reportedly be required to demonstrate a significant reduction in recurrent laryngeal nerve paralysis using IONM [4, 464]. The required number of cases was not reached even in a systematic review (30,926 cases; paralysis rates: 3.18% in the IONM group and 3.83% in the non-IONM group; no significant difference) [465] or a meta-analysis (36,487 nerves; transient paralysis rate: 2.56% in the IONM group and 2.71% in the non-IONM group [OR 0.80; 95%CI 0.65–0.99]; permanent paralysis

rate: 0.78% in the IONM group and 0.96% in the non-IONM group; no significant difference) [466]. Each individual report showed that the frequency of recurrent laryngeal nerve paralysis was lower in the IONM group. Some reports have shown a significant decrease in the frequency of transient recurrent laryngeal nerve paralysis, but no significant decrease in permanent paralysis was observed [467–469].

IONM has been reported as significantly more effective for identifying external branches of the superior laryngeal nerve (83.8–89.2% in the IONM group vs. 17.8–34.3% in the non-IONM group). Regarding decrease in phonation parameters with and without IONM were 2% vs. 10% for maximum phonation time, 2% vs. 13% for voice level, and 1% vs. 9% for fundamental frequency [470, 471].

Many reports have shown that specificity and negative predictive value >99% in identifying vocal cord paralysis after surgery using IONM. Loss of signal identified during surgery using proper methods is highly likely to indicate postoperative vocal cord paralysis or voice disorder [472–474]. IONM requires a dedicated endotracheal tube, a stimulating electrode, a recording device, and other minor equipment. However, the integrity of the recurrent laryngeal nerve can also be confirmed by the surgeon palpating movements of the intrinsic laryngeal muscles with the finger (the laryngeal twitch method) [462]. Use of IONM has been reported to shorten the time required to identify the recurrent laryngeal nerve [475]. Continued use of IONM reduces the frequency of recurrent laryngeal nerve injury [476], and no increase in AEs has been seen in patients with its use [477, 478]. IONM is strongly recommended in cases of malignant tumor surgery accompanied by lymph node dissection, cases involving large nodular goiter, cases of preoperatively suspected vocal cord paralysis, and cases of reoperation, as stated in international guidelines [272, 479]. Active use of IONM may also be considered for surgeons in training [480] and for total thyroidectomy in which both recurrent laryngeal nerves are at risk, from the perspective of medical safety, such as real-time monitoring of nerve damage and avoidance of asphyxiation due to bilateral vocal cord paralysis.

CQ 10-2.

Are pre- and postoperative evaluations of vocal cord movement recommended for thyroid surgery?

Recommendation statement

Evaluations of vocal cord movement by direct observation are recommended before and after all thyroid surgeries.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:**

78%

Outcomes considered

- Detection rate of vocal cord paralysis and laryngeal lesions
- How evaluation of vocal cord paralysis impacts treatment decisions
- Incidence of AEs due to evaluation

Evidence

- The total frequency of preoperative vocal cord paralysis has been reported as 1–6%, and the frequency in patients without dysphonia is 0–0.7%.
- If vocal cord paralysis is confirmed preoperatively, direct observation is useful for diagnosing nerve invasion by cancer, assessing the risk of cancer and considering treatment methods, and planning surgical procedures to avoid bilateral recurrent laryngeal nerve paralysis.
- The frequency of postoperative vocal cord paralysis has been reported as 1.4–38.4% for transient paralysis and 0–18.6% for permanent paralysis after thyroid surgery.
- Dysphonia immediately after surgery is often not due to vocal cord paralysis.
- Postoperative vocal cord paralysis is usually transient.
- Direct observation using laryngeal fiberoptic is the most recommended method for evaluation, and few AEs have been reported.

Summary and discussion of the literature

Causes of vocal disorders during the perioperative period of thyroid surgery include recurrent laryngeal nerve paralysis (vocal cord paralysis), injury to the external branch of the superior laryngeal nerve, injury to the anterior cervical muscles or cricothyroid muscles, edema, vocal cord injury due to endotracheal intubation, scar formation, and arytenoid dislocation. In addition, recurrent laryngeal nerve paralysis may be caused by disorders other than thyroid disease or surgery, such as previous cervical, thoracic, or intracranial surgeries, laryngeal or hypopharyngeal cancer, viral infection, cerebral infarction, diabetic neuropathy, and cranial nerve disorders (cranial nerves IX and X). Vocal cord paralysis is reported to occur in 1–6% of patients preoperatively [481–483]. Most reports have shown that vocal cord paralysis is significantly more common in patients with thyroid cancer than in those with benign tumors [483]. More than half of cases with vocal cord paralysis are reported to occur without dysphonia [483], and vocal cord movements cannot be accurately determined by subjective and objective evaluations of phonation status alone [484]. Vocal cord paralysis is reported in 0–0.7% of patients without dysphonia [483, 485, 486]. On the other hand, 15–87% of patients with thyroid disease are aware of dysphonia [462, 483, 487], so direct

observation is necessary for accurate evaluation of vocal cord movements. For other reasons, such as those listed in Table 19, direct confirmation of vocal cord movement before surgery is useful. Although the frequency of vocal cord paralysis is low among asymptomatic patients, preoperative evaluation of vocal cord movements using laryngeal fiberoptic is simple and minimally invasive, and AEs for patients are rare. Therefore, even considering the burdens for medical professionals and medical economy, direct observation of vocal cord movements before surgery is recommended for all surgical cases. This procedure is considered essential, especially in the cases listed in Table 20.

The frequency of postoperative vocal cord paralysis varies greatly depending on the method of confirmation and the postoperative period, with reports ranging from 1.4% to 38.4% for transient paralysis and from 0% to 18.6% for permanent paralysis [483, 488]. A meta-analysis of more than 25,000 cases reported a rate of 9.8% [489], and a case series of more than 5,000 cases reported a rate of 9% [490], suggesting that vocal cord paralysis occurs in approximately 10% of cases early after surgery [462]. Voice disorders without vocal cord paralysis (vocal cord hemorrhage, laryngitis, laryngeal edema, *etc.*) are frequently observed immediately after surgery [486, 491], so direct evaluation of vocal cord movements within a few days after surgery is essential to determine paralysis. If paralysis is present, the patient should be reexamined every 2–8 weeks. If no improvement is seen within 6 months, the possibility of permanent vocal cord paralysis is considered high, and voice disorder treatment should be considered as necessary.

CQ 10-3.

Is autotransplantation of parathyroid glands unintentionally removed during thyroid surgery recommended?

Recommendation statement

If parathyroid glands are identified in the resected specimen, autotransplantation is recommended to avoid permanent hypoparathyroidism.

Certainty of evidence: C

Strength of recommendation: Strong; **Consensus rate:** 100%

Outcomes considered

- Incidence of transient and permanent hypoparathyroidism
- AEs of parathyroid autotransplantation

Evidence

- Transient and permanent hypoparathyroidism after thyroid surgery have been reported to occur with frequencies of 5–51.9% and 0.5–5.5%, respectively.
- Transient and permanent hypoparathyroidism after autotransplantation have been reported to occur with wide ranges of 4.8–85.2% and 0–22.2%, respectively, due to the wide variability of factors such as the number of parathyroid glands that could be preserved and the number of parathyroid glands transplanted.
- No AEs such as local bleeding due to autotransplantation, disease recurrence due to tissue misidentification, or occurrence of hyperparathyroidism have been reported.

Summary and discussion of the literature

Transient and permanent hypoparathyroidism after thyroid surgery have been reported to occur in 5–51.9% and 0.5–5.5% of cases, respectively [492–494]. Although the incidence varies widely depending on the underlying disease, surgical procedure, evaluation criteria and

Table 19 Reasons why preoperative vocal cord movement assessment is useful

1. Vocal cord paralysis can exist even in the absence of subjective or objective dysphonia.
2. If unilateral vocal cord paralysis is identified preoperatively, a surgical procedure that avoids the risk of nerve damage to the contralateral (healthy) side can be considered.
3. The degree of functional impairment due to cancer invasion into the recurrent laryngeal nerve provides information for selecting treatment methods (extent of thyroidectomy considering adjuvant therapy, nerve preservation by shaving, nerve resection and reconstruction, *etc.*) and for predicting prognosis.
4. Vocal cord paralysis observed postoperatively is useful for determining whether paralysis is due to surgery.

Table 20 Cases in which direct observation of vocal cord movement before surgery is necessary

1. Current or past subjective or objective symptoms of dysphonia
2. Previous neck, thoracic, or head surgery
3. Problems with endotracheal intubation during previous surgery
4. History of neuromuscular disease, cerebrovascular disease, or diabetic neuropathy
5. Surgery for large nodular goiter or mediastinal goiter
6. Surgery for malignant tumors
7. Use of intraoperative nerve stimulator
8. Surgery to expose both recurrent laryngeal nerves (total thyroidectomy, subtotal thyroidectomy, bilateral neck dissection, *etc.*)

timing of determination, hypoparathyroidism occurs at a certain frequency due to impaired blood flow or removal of the parathyroid gland during surgery. In general, hypoparathyroidism occurs more frequently with malignant tumor surgery accompanying lymph node dissection, Graves' disease surgery involving hypermetabolism, and surgery for large benign nodules [494]. Preservation of the parathyroid with function *in situ* is the most effective method to prevent hypoparathyroidism, but when preservation is impossible, parathyroid glands are often identified in the resected specimen and autotransplanted intraoperatively into the sternocleidomastoid muscle, pectoralis major muscle, or a muscle in the forearm.

In cases where preservation of all parathyroid glands *in situ* was not possible and 1–4 glands were autotransplanted, the possibility of avoiding permanent hypoparathyroidism has been reported as high, although transient hypoparathyroidism in the early postoperative period cannot be avoided. In a meta-analysis of 7,291 patients who underwent thyroidectomy, patients who required autotransplantation showed a significantly higher incidence of transient hypoparathyroidism (4.8–85.2%, odds ratio 2.37; 95%CI 1.90–2.96; $p < 0.0001$) than patients who had all glands preserved *in situ*. On the other hand, the incidence of permanent hypoparathyroidism in patients who required autotransplantation was 0–22.2%, not significantly different from the incidence of 0–15.0% in patients with preservation of the entire gland *in situ* and no requirement of autotransplantation (OR 1.17, 95%CI 0.71–1.91; $p = 0.5418$) [493]. In a study of 2,477 patients who underwent total thyroidectomy for thyroid cancer, the incidence of transient hypoparathyroidism in patients who required devascularization or autotransplantation of one or two resected parathyroid glands with parathyroid preservation as much as possible was 46.1%, significantly higher than the 26.5% incidence in patients with preservation of the entire gland, but the incidences of permanent hypoparathyroidism were 1.7% and 0.6%, respectively, showing no significant difference [495]. The incidence of transient hypoparathyroidism increased with the number of parathyroid glands that could not be preserved *in situ* and were unavoidably autotransplanted, but the incidence of permanent hypoparathyroidism was unchanged if two or more glands were autotransplanted. In a study of 5,997 patients who underwent total thyroidectomy, the incidence of permanent hypoparathyroidism when all parathyroid glands could not be preserved was 13.5% in patients with autotransplantation of only one gland. These incidences decreased to 5.2%, 1.8%, and 1.8% in patients with autotransplantation of two, three, or four glands, respectively [496].

PTH was usually significantly lower for up to 1 month after transplantation, but recovered after 6 months and did not change thereafter. Many studies have shown that postoperative PTH levels are lower than preoperatively. Reasons for this include mechanical or thermal damage to the preserved or transplanted parathyroid gland, damage to preserved gland tissue that appears healthy, insufficient blood flow or fibrosis of the transplanted gland, tissue loss during transplantation, and unintended loss of the parathyroid gland [493]. In addition, a study of 154 patients who underwent complementary total thyroidectomy after initial surgery showed permanent hypoparathyroidism in 5%, and autotransplantation was reportedly recommended even during reoperation [497].

Future research questions

In this guideline, the “Certainty of Evidence” for each CQ addressed was generally low. Conducting RCTs for clinical management of thyroid tumors remains challenging due to the required sample size, duration of observation, and associated costs. However, high-quality observational studies, such as prospective studies based on previous retrospective research findings, can also help with the accumulation of more reliable evidence. This will enable improvements in shared decision-making, which is the goal of this guideline, and further the standardization of clinical practice. Finally, the main issues for future revisions are presented as Future Research Questions.

1) Exploring best practices for thyroid nodule diagnosis with a focus on preventing overdiagnosis and overtreatment

In developed countries, improvements in US technology and increased access to screening have highlighted issues of overdiagnosis and overtreatment of PTC. Alongside advances in risk assessment methods for PTC, a shift has been seen away from a one-size-fits-all approach towards the concept of risk-adapted management, leading to a global trend of “less is more” in thyroid cancer care.

This guideline recommends against US screening for thyroid cancer in asymptomatic adults (CQ 1-1). However, when a solid nodule is incidentally discovered, indications for FNAC follow the “Thyroid Ultrasound Diagnostic Guidebook, Revised 3rd edition”, recommending biopsy for nodules over 5 mm when malignancy is strongly suspect based on US findings (Algorithm 1-2).

In Japan, US has long been used in the diagnosis of thyroid nodules. However, compared to guidelines from various countries, which utilize the Thyroid Imaging,

Reporting and Data System for malignancy risk assessment and biopsy recommendations, the diagnostic criteria in Japan seem to have a somewhat less-defined approach. Moving forward, best practices need to be explored in Japan, including the development of standardized US diagnostic categories.

2) Future directions in active surveillance for very low-risk PTC

Active surveillance as a strategy to address the overtreatment of thyroid cancer has produced evidence from Japan that has influenced global guidelines (CQ 2-1). Future research topics include the search for molecular markers to better predict progression of PTCs under surveillance, examination of the effects of TSH suppression therapy on surveillance cases, comparative studies between thermal ablation treatments such as radiofrequency ablation and active surveillance, exploration of the potential for expanding indications for active surveillance to include T1bN0M0 PTCs, and studies on the natural history of low-risk PTC.

3) Care for thyroid cancer survivors

Given the generally favorable prognosis of thyroid cancer, numbers of postoperative patients and those under active surveillance are increasing each year. However, research into the psychological, social, and economic burdens faced by thyroid cancer survivors remains limited. Further studies, including of patient-reported outcomes, are needed to better understand long-term health status from the patient's perspective.

4) Generating evidence for new pathological subtypes of thyroid cancer

In this guideline, treatment strategies for thyroid cancers continue to be organized along traditional histological subtypes. Meanwhile, the 5th edition of the WHO Classification of Tumors of the Thyroid published in 2022 adopted a systematic approach based on the cellular origin and malignancy grade of thyroid tumors. This emphasizes the genetic mutations involved in tumor development and progression, altering the framework and order of pathological classifications to incorporate clinical prognostic factors. Concepts like low-risk neoplasms and high-grade malignancies (such as poorly differentiated and differentiated high-grade thyroid carcinoma) are now included.

The 9th edition of the Japanese General Rules for the Description of Thyroid Cancer, published in 2023, largely aligns with the new WHO classification, reflecting an emphasis on international standards. Moving forward, generating evidence based on these updated classifications will be essential. For example, the concept

of low-risk neoplasms is seen as a measure to curb overdiagnosis and overtreatment in Western countries, but evidence-based assessments of benefits and harms specific to Japan remain undetermined.

5) Challenges in risk classification and risk-adapted management of PTC

This guideline maintains the risk classification for PTC used in the “2018 Thyroid Tumor Management Guidelines”, continuing the approach based on static pre- and intraoperative prognostic factors primarily derived from the TNM classification. This classification does not include age, as alteration of treatment plans based solely on specific age thresholds was deemed inappropriate. Nonetheless, the importance of age as a prognostic factor for PTC has been explicitly noted (Note 2-1). Developing treatment algorithms that consider age and other patient-related factors remains an important task for the future.

Dynamic prognostic factors, such as postoperative Tg and TgAb levels, are also considered in PTC risk classifications (Notes 2-3, 2-4). The 2015 guidelines of the ATA use a “dynamic risk stratification” approach, in which cases are reclassified into four groups—excellent response, biochemical incomplete response, structural incomplete response, and indeterminate response—based on imaging and Tg/TgAb results post-treatment. This helps predict recurrence and disease-specific mortality and guides management. Such classification is mainly applied to patients who have undergone total thyroidectomy and RAI ablation therapy, although evidence from Japan on this approach again remains limited.

For the risk-adapted management of PTC, Algorithm 2-1 strongly recommends active surveillance over lobectomy for the very-low-risk group and lobectomy over total thyroidectomy for the intermediate-risk group. In addition, lobectomy is considered acceptable for young high-risk patients due to the favorable prognosis in this group. Preventive lateral neck dissection is not recommended regardless of risk group (CQ 2-3), and Column 2-3 discusses the omission of prophylactic central neck dissection. These reflect the guiding principles in Japan as a pioneer of the global “less is more” trend, while acknowledging that conventional comprehensive treatment (total thyroidectomy, lymph node dissection, RAI therapy, and TSH suppression) for high-risk PTC may not be fully validated (Column 2-2). Further research is needed to establish treatment sequences that provide equivalent or superior outcomes with reduced burdens on patients, particularly as risk assessments using molecular markers advance.

6) Utility of gene testing kits for preoperative diagnosis of follicular tumors

The preoperative diagnosis of follicular tumors has presented a longstanding challenge. In the United States, commercially available molecular diagnostic kits using cytological specimens reportedly offer a high negative predictive value and may be useful in avoiding overtreatment. However, evidence is limited regarding their accuracy in correctly identifying FTC and guiding surgical decisions. While the potential introduction of these kits into Japan is anticipated, evaluating their utility—and the balance of benefits and harms in particular—will represent an important clinical issue.

7) Novel pharmacotherapies as neoadjuvant treatment for ATC

There is still no established standard treatment for ATC, and treatment outcomes have historically been poor. However, recent developments with BRAF/MEK inhibitors for cases with *BRAF* mutations have shown promise. Notably, favorable outcomes have been reported for patients able to undergo curative resection following such therapy (with or without immune checkpoint inhibitors). Validation of these results in a larger number of cases in Japan is highly anticipated.

8) Optimal balance between surgical treatment and pharmacotherapy for advanced DTC

Tumor invasion in locally advanced DTC often raises concerns about the use of MKIs. While a treatment sequence involving surgical local control followed by MKI therapy is generally preferred, clear evidence in support of this approach remains limited. The emergence of SKIs targeting specific genetic alterations in individual tumors further underscores the need for large-scale studies evaluating the role of surgery and the optimal sequence of treatments.

9) Challenges in treatment with SKIs

The era of cancer genome medicine has finally arrived for thyroid cancer. While thyroid cancer frequently harbors targetable genetic abnormalities, cases eligible for such targeted therapy are still relatively limited. To ensure the correct genetic tests are performed at the appropriate time for the appropriate patients, and to allow administration of SKIs, immune checkpoint inhibitors, and MKIs in an evidence-based sequence, long-term treatment data must be accumulated from a large number of cases.

To maximize patient benefit while maintaining cost-effectiveness in healthcare, improvements are needed to the current system in which CDx vary by drug. Additionally, the development of optimal testing methods remains

a challenge. According to the new WHO classification, tumors originating from follicular thyroid cells are broadly categorized into *RAS*-driven and *BRAF*-driven tumors based on driver mutations. Establishing a standard for genetic testing that is minimally invasive and low cost at the initial diagnosis of thyroid tumors could help address some of these challenges.

10) Establishing multidisciplinary care in thyroid tumor management

With the advent of new drug therapies and from the perspective of medical safety, the era in which endocrine and thyroid surgeons or head-and-neck surgeons alone manage thyroid tumors has drawn to a close. It is now an urgent task to enhance collaboration among oncologists, radiologists, nuclear medicine specialists, endocrinologists, pathologists, and other relevant medical staff, as well as various departments related to adverse drug reactions and medical safety, both within and outside medical facilities. Building expertise in these areas is essential. Japan has a smaller proportion of endocrinologists dedicated to thyroid cancer care compared to other countries, and promoting closer communication with endocrinologists is indispensable.

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